PYRIMIDINE DERIVATIVES AS CANNABINOID RECEPTOR MODULATORS

Compounds

The present invention relates to novel pyrimidine derivatives, pharmaceutical compositions containing these compounds and their use in the treatment of diseases, particularly pain, which diseases are caused directly or indirectly by an increase or decrease in activity of the cannabinoid receptor.

Cannabinoids are a specific class of psychoactive compounds present in Indian cannabis (*Cannabis sativa*), including about sixty different molecules, the most representative being cannabinol, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of cannabis dates back to the ancient dynasties of China, where, 5,000 years ago, cannabis was used for the treatment of asthma, migraine and some gynaecological disorders. These uses later became so established that, around 1850, cannabis extracts were included in the US Pharmacopaeia and remained there until 1947.

Cannabinoids are known to cause different effects on various systems and/or organs, the most important being on the central nervous system and on the cardiovascular system. These effects include alterations in memory and cognition, euphoria, and sedation. Cannabinoids also increase heart rate and vary systemic arterial pressure. Peripheral effects related to bronchial constriction, immunomodulation, and inflammation have also been observed. The capability of cannabinoids to reduce intraocular pressure and to affect respiratory and endocrine systems is also well documented. See e.g. L.E. Hollister, Health Aspects of Cannabis, Pharmacological Reviews, Vol. 38, pp. 1-20, (1986). More recently, it was found that cannabinoids suppress the cellular and humoral immune responses and exhibit antiinflammatory properties. Wirth et al., Antiinflammatory Properties of Cannabichrome, Life Science, Vol. 26, pp. 1991-1995, (1980).

In spite of the foregoing benefits, the therapeutic use of cannabis is controversial, both due to its relevant psychoactive effects (causing dependence and addiction), and due to manifold side effects that have not yet been completely clarified. Although work in this field has been ongoing since the 1940's, evidence indicating that the peripheral effects of cannabinoids are directly mediated, and not secondary to a CNS effect, has been limited by the lack of receptor characterization, the lack of information concerning an endogenous cannabinoid ligand and, until recently, the lack of receptor subtype selective compounds.

The first cannabinoid receptor was found to be mainly located in the brain, in neural cell lines, and, only to a lesser extent, at the peripheral level. In view of its location, it was called the central receptor ("CB1"). See Matsuda et al., "Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA," Nature, Vol. 346, pp. 561-564 (1990. The second cannabinoid receptor ("CB2") was identified in the spleen, and was assumed to modulate the non psychoactive effects of the cannabinoids. See Munro et el., "Molecular Characterization of a Peripheral Receptor for Cannabinoids," Nature, Vol. 365, pp. 61-65 (1993).

Recently, some compounds have been prepared which are capable of acting as agonists on both the cannabinoid receptors. For example, use of derivatives of dihydroxypyrrole-(1,2,3-d,e)-1,4-benzoxazine in the treatment of glaucoma and the use of derivatives of 1,5-diphenyl-pyrazole as immunomodulators or psychotropic agents in the treatment of various neuropathologies, migraine, epilepsy, glaucoma, etc are known. See U.S. Patent No. 5,112,820 and EP 576357, respectively.

However, because these compounds are active on both the CB1 and CB2 receptor, they can lead to serious psychoactive effects.

The foregoing indications and the preferential localization of the CB2 receptor in the immune system confirms a specific role of CB2 in modulating the immune and antiinflammatory response to stimuli of different sources.

The total size of the patient population suffering from pain is vast (almost 300 million), dominated by those suffering from back pain, osteo-arthritic pain and post-operative pain. Neuropathic pain (associated with neuronal lesions such as those induced by diabetes, HIV, herpes infection, or stroke) occurs with lower, but still substantial prevalence, as does cancer pain.

The pathogenic mechanisms that give rise to pain symptoms can be grouped into two main categories:

- those that are components of inflammatory tissue responses (Inflammatory Pain);
- those that result from a neuronal lesion of some form (Neuropathic Pain).

Chronic inflammatory pain consists predominantly of osteoarthritis, chronic low back pain and rheumatoid arthritis. The pain results from acute and on-going injury and/or inflammation. There may be both spontaneous and provoked pain.

There is an underlying pathological hypersensitivity as a result of physiological hyperexcitability and the release of inflammatory mediators which further potentiate this hyperexcitability. CB2 receptors are expressed on inflammatory cells (T cells, B cells, macrophages, mast cells) and mediate immune suppression through inhibition of cellular interaction/ inflammatory mediator release. CB2 receptors may also be expressed on sensory nerve terminals and therefore directly inhibit hyperalgesia.

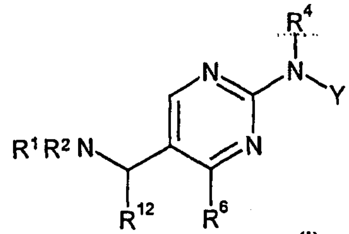
The role of CB2 in immunomodulation, inflammation, osteoporosis, cardiovascular, renal and other disease conditions is now being examined. In light of the fact that cannabinoids act on receptors capable of modulating different functional effects, and in view of the low homology between CB2 and CB1, the importance of developing a class of drugs selective for the specific receptor sub-type is evident. The natural or synthetic cannabinoids currently available do not fulfil this function because they are active on both receptors.

Based on the foregoing, there is a need for compounds which are capable of selectively modulating the receptor for cannabinoids and, therefore, the pathologies associated with such receptors. Thus, CB2 modulators offer a unique approach toward the pharmacotherapy of immune disorders, inflammation, osteoporosis, renal ischemia and other pathophysiological conditions.

The present invention provides novel pyrimidine derivatives of formula (I) and pharmaceutically acceptable derivatives thereof, pharmaceutical compositions containing these compounds or derivatives, and their use as CB2 receptor modulators, which are useful in the treatment of a variety of disorders.

The present invention further comprises a method for treating disease mediated by CB2 receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The invention provides compounds of formula (I):



wherein: (I)

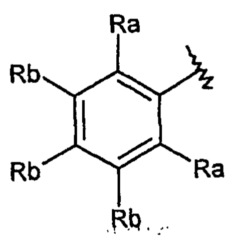
Y is phenyl, unsubstituted or substituted with one, two or three substituents;

R^1 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or halosubstitutedC_{1-6} alkyl;

R^2 is $(CH_2)_mR^3$ where m is 0 or 1;

or R^1 and R^2 together with N to which they are attached form an unsubstituted or substituted 4- to 8- membered non-aromatic heterocyclyl ring;

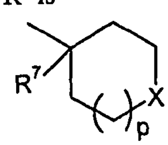
R^3 is hydrogen, an unsubstituted or substituted 4- to 8- membered non-aromatic heterocyclyl group, an unsubstituted or substituted C_{3-8} cycloalkyl group, an unsubstituted or substituted straight or branched C_{1-10} alkyl, an unsubstituted or substituted C_{5-7} cycloalkenyl, R^5; or R^3 is an unsubstituted or substituted 5- to 6- membered aromatic heterocyclyl group, or group A:



(A)

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or halosubstitutedC_{1-6} alkyl, $COCH_3$, or SO_2Me;

R^5 is



wherein p is 0, 1 or 2, and X is CH_2, O, S, SO or SO_2;

R^6 is halo, an substituted or unsubstituted (C_{1-6})alkyl, (C_{3-6})cycloalkyl, 4- to 7- membered non aromatic heterocyclyl group;

R^7 is OH, C_{1-6}alkoxy, $NR^{8a}R^{8b}$, $NHCOR^9$, $NHSO_2R^9$, $SOqR^9$;

R^{8a} is H or C_{1-6}alkyl;

R^{8b} is H or C_{1-6}alkyl;

R^9 is C_{1-6}alkyl;

Ra is independently selected from hydrogen, fluoro, chloro or trifluoromethyl;

Rb is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkoxy, hydroxy, cyano, halo, sulfonyl, $CONH_2$, COOH or $NHCOOC_{1-6}$alkyl;

R^{12} is hydrogen or C_{1-6}alkyl;

q is 0, 1 or 2;

and pharmaceutically acceptable derivatives thereof,

wherein the compound is not (5-{[bis-(2-methoxy-ethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-(3-chlorophenyl)-amine or {1-[2-(3-chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-piperidin-4-yl}-methanol, formate.

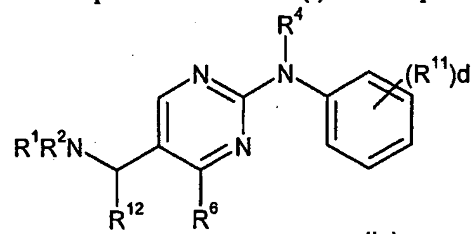
(5-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-(3-chlorophenyl)-amine and {1-[2-(3-chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-piperidin-4-yl}-methanol, formate do not appear to have any potency or efficacy against CB2.

In one embodiment Y is a substituted phenyl. In one embodiment Y is substituted by 1 or 2 substituents.

When Y is substituted, the substituent or substituents may be selected from: C_{1-6} alkyl, halosubstitutedC_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, a C_{1-6}alkyl sulfonyl group, $-CONH_2$,$-NHCOC_{1-6}$alkyl, $-CH_2COOH$, $-COOH$, halosubstituted C_{1-6} alkoxy, SC_{1-6}alkyl or $SO_2NR^{8a}R^{8b}$ wherein R^{8a} and R^{8b} are as defined above.

In one embodiment Y is substituted by halo, cyano, methyl, trifluoromethyl, methoxy or trifluoromethoxy or SCH_3. In one embodiment halo is chloro, fluoro, or bromo.

In one embodiment the compounds of formula (I) are compounds of formula (Ia):



(Ia)

wherein;

R^1 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl and halosubstitutedC_{1-6} alkyl;

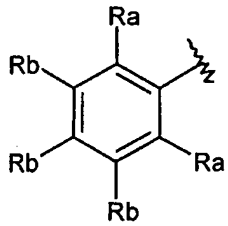
R^2 is $(CH_2)_mR^3$ where m is 0 or 1;

or R^1 and R^2 together with N to which they are attached form a 4- to 8- membered non-aromatic ring selected from azetidinyl, pyrrolidinyl, morpholinyl, piperizinyl, piperidinyl, thiomorpholinyl, tetrahydropyridinyl, azapine, oxapine, azacyclooctanyl, azaoxacyclooctanyl and azathiacyclooctanyl any of which can be unsubstituted or substituted by one, two or three substituents selected from C_{1-6} alkyl, C_{1-6} alkylOH, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, sulfonyl group, methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, (=O), $-CONHCH_3$ and $NHSO_2CH_3$, $C(O)OC_{1-6}$alkyl.

R^3 is hydrogen, 2- or 3- azetidinyl, oxetanyl, thioxetanyl, thioxetanyl-s-oxide, thioxetanyl-s,s-dioxide, dioxalanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophenyl-s-oxide, tetrahydrothiophenyl-s,s-dioxide, morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl-s-dioxide, tetrahydrothiopyranyl-s,s-dioxide, thiomorpholinyl, thiomorpholinyl-s,s-dioxide, tetrahydropyridinyl, dioxanyl, tetrahydrothiopyran 1,1 dioxide, azapine, oxapine, azacyclooctanyl, azaoxacyclooctanyl, azathiacyclooctanyl, oxacylcooctanyl, thiacyclooctanyl, a C_{3-8} cycloalkyl group, a straight or branched C_{1-10} alkyl, a C_{5-7} cycloalkenyl or R^5, any of which can be unsubstituted or substituted by one, two or three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, sulfonyl

group, methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, (=O), and $-CONHCH_3$ and when R^3 is alkyl it can be phenyl or phenyl substituted by halo, hydroxy or cyano;

or R^3 is group A or selected from furanyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thienyl, pyrazolyl, tetrazolyl, pyridinyl, pyrizinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl any of which can be unsubstituted or substituted by one, two or three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, sulfonyl group, methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, (=O), and $-CONHCH_3$;

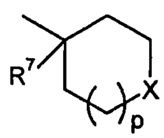


(A)

R^{11} is selected from C_{1-6} alkyl, halosubstitutedC_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, a C_{1-6}alkyl sulfonyl group, $-CONH_2$, $-NHCOC_{1-6}$alkyl, -COOH, $-CH_2COOH$, halosubstitutedC_{1-6} alkoxy, SC_{1-6}alkyl and $SO_2NR^{8a}R^{8b}$;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or halosubstitutedC_{1-6} alkyl, $COCH_3$, and SO_2Me;

R^5 is



wherein p is 0, 1 or 2 and X is CH_2, O, S, SO or SO_2;

R^6 is halo, a substituted or unsubstituted (C_{1-6})alkyl, (C_{3-6})cycloalkyl, 4- to 7- membered non aromatic heterocyclyl group;

R^7 is OH, C_{1-6}alkoxy, $NR^{8a}R^{8b}$, $NHCOR^9$, $NHSO_2R^9$, $SOqR^9$;

R^{8a} is H or C_{1-6}alkyl;

R^{8b} is H or C_{1-6}alkyl;

R^9 is C_{1-6}alkyl;

R^{12} is hydrogen or C_{1-6}alkyl;

Ra is independently selected from hydrogen, fluoro, chloro or trifluoromethyl;

Rb is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkoxy, hydroxy, cyano, halo, sulfonyl, $CONH_2$, COOH or $NHCOOC_{1-6}$alkyl;

q is 0, 1 or 2;

d is 0, 1, 2 or 3

and pharmaceutically acceptable derivatives thereof

wherein the compound is not

(5-{[bis-(2-methoxy-ethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-(3-chlorophenyl)-amine or {1-[2-(3-chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-piperidin-4-yl}-methanol, formate.

In one embodiment R^1 is hydrogen or methyl.

In one embodiment R^4 is C_{1-6} alkyl or hydrogen, suitably methyl or hydrogen, even more suitably hydrogen.

In one embodiment R^6 is C_{1-6}alkyl, (C_{3-6})cycloalkyl or CF_3.

In one embodiment R^7 is OH.

In one embodiment X is CH_2.

In one embodiment, R^3 is an unsubstituted or substituted 4- to 8- membered non-aromatic heterocyclyl group, an unsubstituted or substituted C_{3-8} cycloalkyl group, an unsubstituted or substituted straight or branched C_{1-10} alkyl, an unsubstituted or substituted C_{5-7} cycloalkenyl, R^5; or R^3 is an optionally substituted 5- to 6- membered aromatic heterocyclyl group, or group A.

In one embodiment when R^3 is an optionally substituted C_{3-8}cycloalkyl group or an optionally substituted 4- to 8- membered nonaromatic heterocyclyl group, an unsubstituted or substituted 5- to 6- membered aromatic heterocyclyl group, or group A, m is 1.

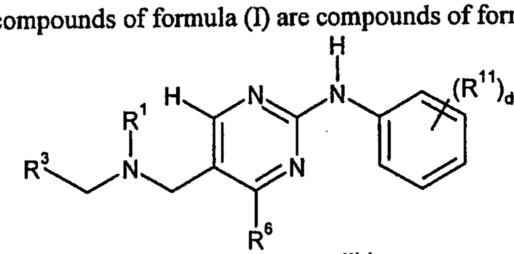
In one embodiment R^2 is CH_2R_3.

In one embodiment R^{12} is hydrogen.

In one embodiment R^3 is an unsubstituted or substituted 4- to 8- membered non-aromatic heterocyclyl group or group A, pyridinyl, or pyrimidinyl, any of which can be optionally substituted.

In one embodiment R^1 and R^2 together with N to which they are attached form a 4- to 8- membered non- aromatic ring selected from azetidinyl, pyrrolidinyl, morpholinyl, piperizinyl, piperidinyl, tetrahydropyridinyl, azapine, oxapine, azacyclooctanyl, azaoxacyclooctanyl and azathiacyclooctanyl.

In one embodiment compounds of formula (I) are compounds of formula (Ib):



(Ib)

R^1 is hydrogen or methyl

R^3 is an unsubstituted or substituted 4- to 8- membered non-aromatic heterocyclyl group an unsubstituted or substituted C_{3-8} cycloalkyl group, an unsubstituted or substituted straight or branched C_{1-10} alkyl;

R^6 is an substituted or unsubstituted (C_{1-6})alkyl, (C_{3-6})cycloalkyl, or 4- to 7- membered non aromatic heterocyclyl group;

R^{11} is selected from halo, cyano, methyl, trifluoromethyl, methoxy, trifluoromethoxy or SCH_3;

d is 0, 1, 2 or 3;

and pharmaceutically acceptable derivatives thereof wherein the compound is not

{1-[2-(3-chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-piperidin-4-yl}-methanol, formate.

In one embodiment R^3 is cyclobutyl or cyclopropylmethyl.

In one embodiment R^6 is isopropyl, cyclopropyl, tert-butyl or trifluoromethyl.

In one embodiment R^6 is isopropyl, cyclopropyl or trifluoromethyl.

In one embodiment R^1 is hydrogen.

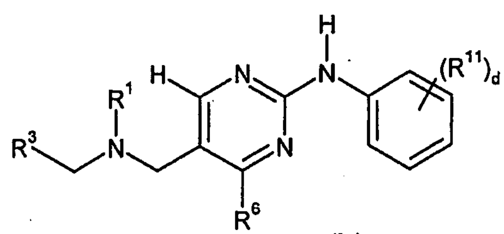
In one particular embodiment R^1 and R^2 together with N to which they are attached form a 4- to 8- membered non-aromatic heterocyclyl ring which is selected from pyrrolidinyl, morpholinyl, piperizinyl, piperidinyl and tetrahydropyridinyl.

In one particular embodiment when R^3 is nonaromatic heterocyclyl it is selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophenyl-s-oxide, tetrahydrothiophenyl-s,s-dioxide morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiomorpholinyl, thiomorpholinyl-s,s-dioxide, tetrahydropyridinyl.

When R^1 and R^2 together with N to which they are attached form a 4- to 8- membered non-aromatic heterocyclyl ring which is substituted, or when R^3 is substituted, the substituent or substituents may be selected from: C_{1-6} alkyl, C_{1-6} alkyl-OH, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo or a sulfonyl group, methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, (=O), $CONHCH_3$ and $NHSO_2CH_3$, $C(O)OC_{1-6}$alkyl wherein R^{8a} and R^{8b} are as described above. Additionally when R^3 is C_{1-6} straight or branched alkyl it can be substituted by optionally substituted phenyl, wherein the substituents can be selected from halo, hydroxy or cyano .

When R^1 and R^2 together with N to which they are attached form a 4- to 8- membered non-aromatic heterocyclyl ring which is substituted, or when R^3 is substituted there can be 1, 2 or 3 substituents.

In one embodiment compounds of formula (I) can be selected from compounds of formula (Ic):

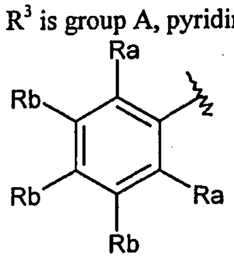


(Ic)

wherein

R^1 is hydrogen or methyl.

R^3 is group A, pyridinyl, or pyrimidinyl, any of which can be optionally substituted;



(A)

Ra is independently selected from hydrogen, fluoro, chloro or trifluoromethyl;

Rb is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkoxy, hydroxy, cyano, halo, sulfonyl, $CONH_2$, COOH or $NHCOOC_{1-6}$alkyl;

R^6 is an substituted or unsubstituted (C_{1-6})alkyl, (C_{3-6})cycloalkyl or 4- to 7- membered non aromatic heterocyclyl group;

R^{11} is selected from halo, cyano, methyl, trifluoromethyl, methoxy, trifluoromethoxy SCH_3;

d is 0, 1, 2 or 3;

and pharmaceutically acceptable derivatives thereof.

Alternatively R^1 is hydrogen.

When R^6 is substituted by 1, 2 or 3 substitutents the substituent or substituents may be selected from OH, halo, cyano, C_{1-6}alkoxy, $NR^{8a}R^{8b}$, $NHCOR^9$, $NHSO_2R^9$, $SOqR^9$; wherein R^{8a}, R^{8b}, R^9, and q are defined above.

When R^1 and R^2 taken together with the N to which they are attached form an optionally substituted non-aromatic heterocyclyl ring, the ring may optionally contain 1, 2, 3 or 4 further hetero atoms. The ring may be saturated or unsaturated. In one embodiment the further hetero atoms are selected from oxygen, nitrogen or sulphur. An example of a 4 membered heterocyclyl ring is azetidinyl Examples of 5- membered heterocyclyl rings include pyrrolidinyl, Examples of 6-membered heterocyclyl rings are morpholinyl, piperizinyl, piperidinyl or tetrahydropyridinyl. An additional example is thiomorpholinyl. Examples of a 7- membered heterocyclyl ring are azapine or oxapine. Examples of 8-membered heterocyclyl rings are azacyclooctanyl, azaoxacyclooctanyl or azathiacyclooctanyl.

When R^3 or R^6 is an optionally substituted non-aromatic heterocyclyl group, the ring may contain 1, 2, 3, or 4 hetero atoms. In one embodiment the hetero atoms are selected from oxygen, nitrogen or sulphur. Examples of 4- membered groups are 2- or 3- azetidinyl, oxetanyl, thioxetanyl, thioxetanyl-s-oxide and thioxetanyl-s,s-dioxide. Examples of 5- membered heterocyclyl groups in this instance include dioxalanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophenyl-s-oxide and tetrahydrothiophenyl-s,s-dioxide. Examples of 6-membered heterocyclyl groups are morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl-s-dioxide, tetrahydrothiopyranyl-s,s-dioxide, thiomorpholinyl, thiomorpholinyl-s,s-dioxide, tetrahydropyridinyl dioxanyl, and tetrahydro-thiopyran 1,1 dioxide. Examples of a 7- membered heterocyclyl ring are azapine or oxapine. Examples of 8- membered groups are azacyclooctanyl, azaoxacyclooctanyl or azathiacyclooctanyl, oxacylcooctanyl, or thiacyclooctanyl.

When R^3 is an unsubstitited or substituted aromatic heterocyclyl group, the ring may contain 1, 2, 3, or 4 hetero atoms. In one embodiment the hetero atoms are selected from oxygen, nitrogen or sulphur. Examples of 5- membered heterocyclyl groups in this instance include furanyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thienyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridinyl, pyrizinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl.

In one embodiment the compounds of formula (I) are selective for CB2 over CB1. In one embodiment the compounds are 100 fold selective i.e. compounds of formula (I) have an EC50 value at the cloned human cannabinoid CB2 receptor of at least 100 times the EC50 values at the cloned human cannabinoid CB1 receptor or have less than 10% efficacy at the CB1 receptor.

The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable-derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the physiological acceptable salts thereof. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse , J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" includes salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, trishydroxylmethyl amino methane, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

Suitable examples of pharmaceutically acceptable salts include the ammonium, calcium, magnesium, potassium, and sodium salts, and those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, hydrochloric, sulfuric, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms 'halogen or halo' are used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, or combinations thereof.

The term 'alkoxy' as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-

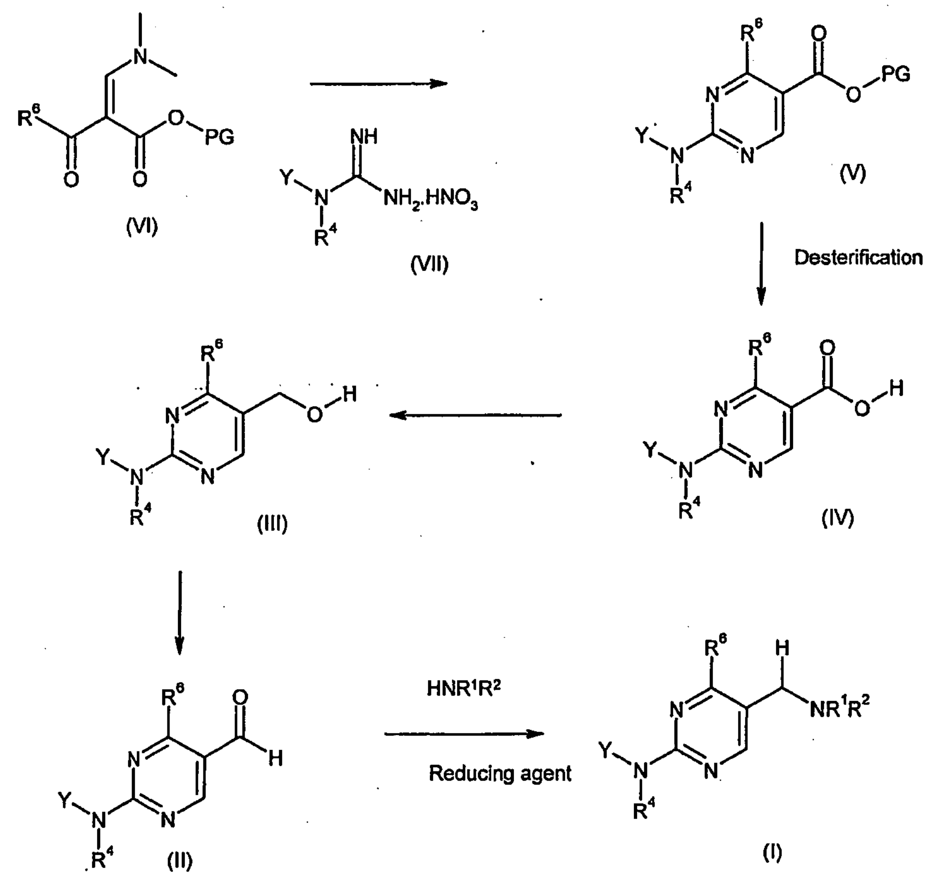
propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group.

The term 'cycloalkyl' means a closed 4- to 8- membered non-aromatic ring, for example cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or cyclooctyl.

The term 'cycloalkenyl" as a group or part of a group means a non-aromatic ring, containing at least one CH=CH moiety for example cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, or cyclooctenyl.

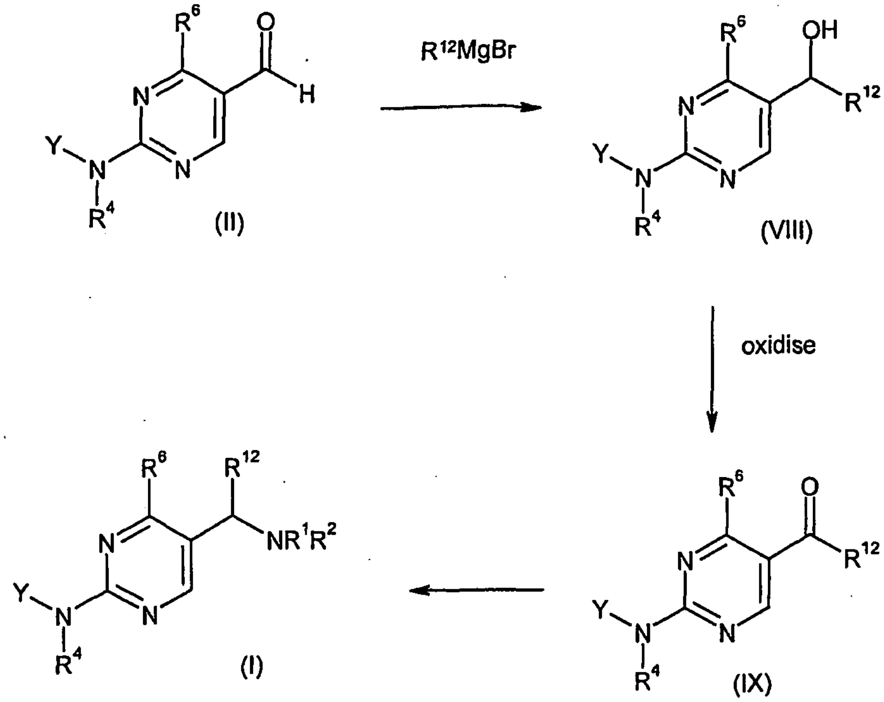
The term 'aryl' means a 5- or 6- membered aromatic ring, for example phenyl, or a 7- to 12-membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl.

Compounds of formula (I) when R^{12} is H can be prepared as set forth in the following scheme:



wherein PG is a protecting group for example methyl, ethyl or benzyl, and R^1, R^2, R^4, R^6, and Y are as defined for compounds of formula (I).

Compounds of formula (I) where R^{12} is other than hydrogen can be prepared by the following scheme from compounds of formula (II) (prepared as set out in scheme 1):



wherein R^1, R^2, R^4, R^6, R^{12} and Y are as defined for compounds of formula (I) except R^{12} is not hydrogen.

It is to be understood that the present invention encompasses all isomers of compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I.

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{8}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic

advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

The compounds of the invention may bind selectively to the CB2 receptor, may therefore be useful in treating CB2 receptor mediated diseases.

In view of their ability to bind to the CB2 receptor, the compounds of the invention may be useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) may be useful as analgesics. For example they may be useful in the treatment of chronic inflammatory pain (e.g. pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention may also be useful disease modification or joint structure preservation in multiple sclerosis, rheumatoid arthritis, osteo-arthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) may also be useful in the treatment of bladder hyperrelexia following bladder inflammation.

The compounds of formula (I) may also be useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) may also be effective in increasing the latency of HIV infection.

The compounds of formula (I) may also be useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) may also be useful in the treatment of neuritis, heart burn, dysphagia, pelvic hypersensitivity, urinary incontinence, cystitis or pruritis.

The compounds of formula (I) may also be useful for the preparation of a drug with diuretic action.

The compounds of formula (I) may also be useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) may also be useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) may also be useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); dementia in Parkinson's disease ; metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment. The compounds may also be useful for the treatment of amyotrophic lateral sclerosis (ALS) and neuroinflamation.

The compounds of formula (I) may also be useful in neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) may also be useful in the treatment of tinnitus.

The compounds of formula (I) may also be useful in the treatment of psychiatric disease for example schizophrenia, depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety disorders (including generalised anxiety disorder and social anxiety disorder), panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof.

The compounds of formula (I) may also be useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) may also be useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

The term "treatment" or "treating" as used herein includes the treatment of established disorders and also includes the prophylaxis thereof. The term " prophylaxis" is used herein to mean preventing symptoms in an already afflicted subject or preventing recurrance of symptoms in an afflicted subject and is not limited to complete prevention of an afflication.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the activity of cannabinoid 2 receptors.

According to a further aspect of the invention, we provide a method of treating a mammal including a human subject suffering from a condition which is mediated by the activity of cannabinoid 2 receptors which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a mammal including a human subject suffering from an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

In one embodiment the pain is selected from inflammatory pain, viseral pain, cancer pain, neuropathic pain, lower back pain, muscular sceletal, post-operative pain, acute pain and migraine. For example, the inflammatory pain is pain associated with rheumatoid arthritis or osteoarthritis.

According to one aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use as a medicament in the treatment of pain.

According to another aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis.

In order to use a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect of the invention is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

As used herein, "modulator" means both antagonist, partial or full agonist and inverse agonist. In one embodiment the present modulators are agonists.

Compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parentarally, sub-lingually, dermally, intranasally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, olive oil, glycerine, glucose (syrup) or water with a flavouring, suspending, or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers or a semi solid e.g. mono di-glycerides of capric acid, Gelucire™ and Labrasol™, or a hard capsule shell e.g gelatin. Where the composition is in the form of a soft shell capsule e.g. gelatin, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums or oils, and are incorporated in a soft capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or derivative in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable derivative thereof which is active when administered in this way, with

a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

In one embodiment the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 mg to 500 mg/Kg, and for example, from 0.01 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg to 100 mg/Kg, of a compound of formula(I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and for example, 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 1000 mg/Kg, of a compound of formula(I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 200 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

It may be advantageous to prepare the compounds of the present invention as nanoparticles. This may improve the oral bioavailability of the compounds. For the purposes of the present invention "nanoparticulate" is defined as solid particles with 50% of the particles having a particle size of less than 1μm, for example less than 0.75μm

The particle size of the solid particles of compound (I) may be determined by laser diffraction. A suitable machine for determining particle size by laser diffraction is a Lecotrac laser particle size analyser, using an HELOS optical bench fitted with a QUIXEL dispersion unit.

Numerous processes for the synthesis of solid particles in nanoparticulate form are known. Typically these processes involve a milling process, for example a wet milling process in the presence of a surface modifying agent that inhibits aggregation and/or crystal growth of the nanoparticles once created. Alternatively these processes may involve a precipitation process, for example, a process of precipitation in an aqueous medium from a solution of the drug in a non-aqueous solvent.

Accordingly, in a further aspect, the present invention provides a process for preparing compound (I) in nanoparticulate form as hereinbefore defined, which process comprises milling or precipitation.

Representative processes for the preparation of solid particles in nanoparticulate form are described in the patents and publications listed below.

U.S. Patent No. 4,826,689 to Violanto & Fischer, U. S. Patent No. 5,145,684 to Liversidge et al
U.S Patent No. 5,298,262 to Na & Rajagopalan, U.S. Patent No. 5,302,401 Liversidge et al
U.S. Patent No. 5,336,507 to Na & Rajagopalan, U.S. Patent No. 5,340,564 to Illig & Sarpotdar
U.S. Patent No. 5,346,702 to Na Rajagopalan, U.S. Patent No. 5,352,459 to Hollister et al

U.S. Patent No. 5,354,560 to Lovrecich, U.S. Patent No. 5,384,124 to Courteille et al, U.S. Patent No. 5,429,824 to June, U.S. Patent No. 5,503,723 to Ruddy et al, U.S. Patent No. 5,510 118 to Bosch et al, U.S. Patent No. 5,518 to Bruno et al, U.S. Patent No. 5,518,738 to Eickhoff et al, U.S. Patent No. 5,534,270 to De Castro, U.S. Patent No. 5,536,508 to Canal et al, U.S. Patent No. 5,552,160 to Liversidge et al, U.S. Patent No. 5,560,931 to Eickhoff et al, U.S. Patent No. 5,560,932 to Bagchi et al, U.S. Patent No. 5,565,188 to Wong et al, U.S. Patent No. 5,571,536 to Eickhoff et al, U.S. Patent No. 5,573,783 to Desieno & Stetsko, U.S Patent No. 5,580,579 to Ruddy et al, U.S. Patent No 5,585,108 to Ruddy et al, U.S. Patent No. 5,587,143 to Wong, U.S. Patent No. 5,591456 to Franson et al, U.S. Patent No. 5,622,938 to Wong, U.S. Patent No 5,662,883 to Bagchi et al, U.S. Patent No. 5,665,331 to Bagchi et al, U.S Patent No. 5,718,919 to Ruddy et al, U.S. Patent No. 5,747,001 to Wiedmann et al, WO93/25190, WO96/24336, WO 97/14407, WO 98/35666, WO 99/65469, WO 00/18374, WO 00/27369, WO 00/30615 and WO 01/41760.

Such processes may be readily adapted for the preparation of compound (I) in nanoparticulate form. Such processes form a further aspect of the invention.

The process of the present invention for example, uses a wet milling step carried out in a mill such as a dispersion mill in order to produce a nanoparticulate form of the compound. The present invention may be put into practice using a conventional wet milling technique, such as that described in Lachman *et al.*, The Theory and Practice of Industrial Pharmacy, Chapter 2, "Milling" p.45 (1986).

In a further refinement, WO02/00196 (SmithKline Beecham plc) describes a wet milling procedure using a mill in which at least some of the surfaces are made of nylon (polyamide) comprising one or more internal lubricants, for use in the preparation of solid particles of a drug substance in nanoparticulate form.

In another aspect the present invention provides a process for preparing compounds of the invention in nanoparticulate form comprising wet milling a suspension of compound in a mill having at least one chamber and agitation means, said chamber(s) and/or said agitation means comprising a lubricated nylon, as described in WO02/00196.

The suspension of a compound of the invention for use in the wet milling is typically a liquid suspension of the coarse compound in a liquid medium. By "suspension" is meant that the compound is essentially insoluble in the liquid medium. Representative liquid media include an aqueous medium. Using the process of the present invention the average particle size of coarse compound of the invention may be up to 1mm in diameter. This advantageously avoids the need to pre-process the compound.

In a further aspect of the invention the aqueous medium to be subjected to the milling comprises compound (I) present in from about 1% to about 40% w/w, for example, from about 10% to about 30% w/w, more In one embodiment about 20% w/w.

The aqueous medium may further comprise one or more pharmaceutically acceptable water-soluble carriers which are suitable for steric stabilisation and the subsequent processing of compound (I) after milling to a pharmaceutical composition, e.g. by spray drying. Pharmaceutically acceptable excipients most suitable for steric stabilisation and spray-drying are surfactants such as poloxamers, sodium lauryl sulphate and polysorbates etc; stabilisers such as celluloses e.g. hydroxypropylmethyl cellulose; and carriers such as carbohydrates e.g. mannitol.

In a further aspect of the invention the aqueous medium to be subjected to the milling may further comprise hydroxypropylmethyl cellulose (HPMC) present from about 0.1 to about 10% w/w. The process of the present invention may comprise the subsequent step of drying compound of the invention to yield a powder.

Accordingly, in a further aspect, the present invention provides a process for preparing a pharmaceutical composition containing a compound of the present invention which process comprises producing compound of formula (I) in nanoparticulate form optionally followed by drying to yield a powder.

A further aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable deriviate thereof in which the compound of formula (I) or a pharmaceutically acceptable deriviate thereof is present in solid particles in nanoparticulate form, in admixture with one or more pharmaceutically acceptable carriers or excipients.

By "drying" is meant the removal of any water or other liquid vehicle used during the process to keep compound of formula (I) in liquid suspension or solution. This drying step may be any process for drying known in the art, including freeze drying, spray granulation or spray drying. Of these methods spray drying is particularly preferred. All of these techniques are well known in the art. Spray drying/fluid bed granulation of milled compositions is carried out most suitably using a spray dryer such as a Mobile Minor Spray Dryer [Niro, Denmark], or a fluid bed drier, such as those manufactured by Glatt, Germany.

In a further aspect the invention provides a pharmaceutical composition as hereinbefore defined, in the form of a dried powder, obtainable by wet milling solid particles of compound of formaula (I) followed by spray-drying the resultant suspension.

In one embodiment, the pharmaceutical composition as hereinbefore defined, further comprises HPMC present in less than 15% w/w, for example, in the range 0.1 to 10% w/w.

The CB_2 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as aspirin, diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP_1 receptor ligands, EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; bradykinin receptor ligands and vanilloid receptor ligand, antirheumatoid arthritis drugs, for example anti TNF drugs e.g. enbrel, remicade, anti-IL-1 drugs, or DMARDS e.g. leflunamide. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The compounds of the present invention may be administered in combination with other active substances such as 5HT3 antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compound of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compound of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compound of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compound of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

Compounds of the present invention may be used in combination with PDE4 inhibitors. The PDE4 inhibitor useful in this invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act in as PDE4 inhibitor, and which is only or essentially only a PDE4 inhibitor, not compounds which inhibit to a degree of exhibiting a therapeutic effect other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 antagonist which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. Compounds of the present invention or combinations with PDE4 can be used in treating inflammation and as bronchodilators.

It turns out that there are at least two binding forms on human monocyte recombinant PDE 4 (hPDE 4) at which inhibitors bind. One explanation for these observations is that hPDE 4 exists in two distinct forms. One binds the likes of rolipram and denbufylline with a high affinity while the other binds these compounds with a low affinity. The preferred PDE4 inhibitors of for use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE 4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

Reference is made to U.S. patent 5,998,428, which describes these methods in more detail. It is incorporated herein in full as though set forth herein.

Most suitable are PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0.

A further aspect of the invention is an CB2 modulator in combination with a PDE4 inhibitor and pharmaceutical compositions comprising said combination.

A further aspect of the invention is a method of treating lung disorders for example asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD) and cough or a disorder which can be treated with a broncodilator which comprises administering to a mammal including man, an effective amount of a CB modulator or a pharmaceutically acceptable derivative therefore and an effective amount of a PDE4 inhibitor or a pharmaceutically acceptable derivative thereof.

An additional aspect of the invention is the use of an effective amount of a CB2 modulator or a pharmaceutically acceptable derivative therefore and an effective amount of a PDE4 inhibitor or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament in the treatment of lung disorders for example asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD) and cough or for the manufacture of a brocodilator.

When used herein cough can have a number of forms and includes productive, non-productive, hyper-reactive, asthma and COPD associated.

A further aspect of the invention is a patient pack comprsing an effective amount of a CB2 modulator or a pharmaceutically acceptable derivative therefore and an effective amount of a PDE4 inhibitor or a pharmaceutically acceptable derivative

Suitable PDE4 compounds are *cis* [cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate] also known as cilomilast or Ariflo®, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, and *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. They can be made by the processed described in US patents 5,449,686 and 5,552,438. Other PDE4 inhibitors, specific inhibitors, which can be used in this invention are AWD-12-281 from ASTA MEDICA (Hofgen, N. *et al.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787; Parke-Davis/Warner-Lambert); a benzodioxole derivative Kyowa Hakko disclosed in WO 9916766; V-11294A from Napp (Landells, L.J. *et al.* Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12(Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO 99/47505) from Byk-Gulden (now Altana); or a compound identified as T-440 (Tanabe Seiyaku; Fuji, K. et al. *J Pharmacol Exp Ther*, **1998**, 284(1): 162).

Additional PDE4 inhibitors are disclosed on pages 2 to 15 of WO01/13953. Specifically selected are arofylline, atizoram, BAY-19-8004, benafentrine, BYK-33043, CC-3052, CDP-840, cipamfylline, CP-220629, CP-293121, D-22888, D-4396, denbufylline, filaminast, GW-3600, ibudilast, KF-17625, KS-506-G, laprafylline, NA-0226A, NA-23063A, ORG-20241, ORG-30029, PDB-093, pentoxifylline, piclamilast, rolipram, RPR-117658, RPR-122818, RPR-132294, RPR-132703, RS-17597, RS-25344-000, SB-207499, SB210667, SB211572, SB-211600, SB212066, SB212179, SDZ-ISQ-844, SDZ-MNS-949, SKF-107806, SQ-20006, T-2585, tibenelast, tolafentrine, UCB-29646, V-11294A, YM-58997, YM-976 and zardaverine.

In one embodiment the PDE4 inhibitor is selected from cilomilast, AWD-12-281, NCS-613, D-4418, CI-1018, V-11294A, roflumilast or T-440.

It will be appreciated that the compounds of any of the above combinations or compositions may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Determination of cannabinoid CB1 Receptor Agonist Activity

The cannabinoid CB1 receptor agonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

Yeast (*Saccharomyces cerevisiae*) cells expressing the human cannabinoid CB1 receptor were generated by integration of an expression cassette into the *ura3* chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human CB1 receptor flanked by the yeast GPD promoter to the 5' end of CB1 and a yeast transcriptional terminator sequence to the 3' end of CB1. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of Gpa1 are replaced with the C-terminal 5 amino acids of human Gαi3 (as described in Brown *et al.* (2000), *Yeast* **16**:11-22). Cells were grown at 30°C in liquid Synthetic Complete (SC) yeast media (Guthrie and Fink (1991), Methods in Enzymology, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD_{600}/ml).

Agonists were prepared as 10 mM stocks in DMSO. EC_{50} values (the concentration required to produce 50% maximal response) were estimated using dilutions of between 3- and 5-fold (BiomekFX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black, clear bottom, microtitre plates from NUNC (96- or 384-well). Cells were suspended at a density of 0.2 OD_{600}/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 10mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 20μM fluorescein di-β-D-glucopyranoside (FDGlu). This mixture (50ul per well for 384-well plates, 200ul per well for 96-well plates) was added to agonist in the assay plates (Multidrop 384, Labsystems). After incubation at 30°C for 24 hours, fluorescence resulting from degradation

of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-stimulated cell growth, was determined using a Spectrofluor microtitre plate reader (Tecan; excitation wavelength: 485nm; emission wavelength: 535nm). Fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter fit to generate a concentration effect value. Efficacy (E_{max}) was calculated from the equation

$$E_{max} = Max_{[compound\ X]} - Min_{[compound\ X]} / Max_{[HU210]} - Min_{[HU210]} \times 100\%$$

where $Max_{[compound\ X]}$ and $Min_{[compound\ X]}$ are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and $Max_{[HU210]}$ and $Min_{[HU210]}$ are the fitted maximum and minimum respectively from the concentration effect curve for (6aR,10aR)-3-(1,1'-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU210; available from Tocris). Equieffective molar ratio (EMR) values were calculated from the equation

$$EMR = EC_{50\ [compound\ X]} / EC_{50\ [HU210]}$$

Where $EC_{50\ [compound\ X]}$ is the EC_{50} of compound X and $EC_{50\ [HU210]}$ is the EC_{50} of HU210.

Compounds of the Examples tested according to this method had EC50 values >1, 000nM and/or efficacy values <50% at the cloned human CB1 receptor, except for Examples 89 and 91, which had EC50 values of 300-1000nM and efficacies of between 50-100% at the cloned human CB1receptor

Determination of cannabinoid CB2 Receptor Agonist Activity

The cannabinoid CB2 receptor agonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

Yeast (*Saccharomyces cerevisiae*) cells expressing the human cannabinoid CB2 receptor were generated by integration of an expression cassette into the *ura3* chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human CB2 receptor flanked by the yeast GPD promoter to the 5' end of CB2 and a yeast transcriptional terminator sequence to the 3' end of CB2. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of Gpa1 are replaced with the C-terminal 5 amino acids of human Gαi3 (as described in Brown *et al.* (2000), *Yeast* **16**:11-22). Cells were grown at 30°C in liquid Synthetic Complete (SC) yeast media (Guthrie and Fink (1991), Methods in Enzymology, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD_{600}/ml).

Agonists were prepared as 10 mM stocks in DMSO. EC_{50} values (the concentration required to produce 50% maximal response) were estimated using dilutions of between 3- and 5-fold (BiomekFX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black, clear bottom, microtitre plates from NUNC (96- or 384-well). Cells were suspended at a density of 0.2 OD_{600}/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 10mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 20M fluorescein di-β-D-glucopyranoside (FDGlu). This mixture (50ul per well for 384-well plates, 200ul per well for 96-well plates) was added to agonist in the assay plates (Multidrop

384, Labsystems). After incubation at 30°C for 24 hours, fluorescence resulting from degradation of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-stimulated cell growth, was determined using a Spectrofluor microtitre plate reader (Tecan; excitation wavelength: 485nm; emission wavelength: 535nm). Fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter fit to generate a concentration effect value. Efficacy (E_{max}) was calculated from the equation

$$E_{max} = Max_{[compound\ X]} - Min_{[compound\ X]} / Max_{[HU210]} - Min_{[HU210]} \times 100\%$$

where $Max_{[compound\ X]}$ and $Min_{[compound\ X]}$ are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and $Max_{[HU210]}$ and $Min_{[HU210]}$ are the fitted maximum and minimum respectively from the concentration effect curve for (6aR,10aR)-3-(1,1'-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU210; available from Tocris). Equieffective molar ratio (EMR) values were calculated from the equation

$$EMR = EC_{50\ [compound\ X]} / EC_{50\ [HU210]}$$

Where $EC_{50\ [compound\ X]}$ is the EC_{50} of compound X and $EC_{50\ [HU210]}$ is the EC_{50} of HU210.

The compounds of Example 1 to 11, 13 to 38 and 85 to 95 and 97 to 103 tested according to this method had an EC_{50} values of < 300nM and efficacy value of >50% at the cloned human cannabinoid CB2 receptor.

The compounds of Examples 12, 39 to 59 and 96 tested according to this method had an EC_{50} values between 300nM and 1000nM and efficacy value of >50% at the cloned human cannabinoid CB2 receptor.

The compounds of Example 60 to 82, 104 and 105 tested according to this method had an EC_{50} values between >1000nM and/or an efficacy value of <50% at the cloned human cannabinoid CB2 receptor.

The compounds of Examples 83 and 84 had no appreciable potency or efficacy at the CB2 receptor.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

Conditions, Hardware, and Software used for Mass-directed Autopurification

Hardware

Waters 600 gradient pump, Waters 2700 sample manager , Waters Reagent Manager, Micromass ZMD mass spectrometer, Gilson 202 - fraction collector, Gilson Aspec - waste collector.

Software

Micromass Masslynx version 3.5

Column

The column used is typically a Supelco ABZ+ column whose dimensions are 10mm internal diameter by 100mm in length. The stationary phase particle size is 5μm.

Solvents

A. Aqueous solvent = Water + 0.1% Formic Acid

B. Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid

Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate

Needle rinse solvent = MeOH: Water: DMSO 80:10:10

Methods

Five methods are used depending on the analytical retention time of the compound of interest. They all have a flow rate of 20ml/min and a 15-minute runtime, which comprises of a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

Method 1 MDP 1.5-2.2 = 0-30%B
Method 2 MDP 2.0-2.8 = 5-30% B
Method 3 MDP 2.5-3.0 = 15-55%B
Method 4 MDP 2.8-4.0 = 30-80% B
Method 5 MDP 3.8-5.5 = 50-90% B

Conditions used for Analytical LCMS Systems

Hardware

Agilent 1100 gradient pump
Agilent 1100 Autosampler
Agilent 1100 PDA Dectector
Agilent 1100 Degasser
Micromass ZQ mass spectrometer
PL-ELS 1000

Software

Micromass Masslynx versions 3.5/4.0

Column

The column used is a Supelcosil ABZ+PLUS, the dimensions of which are 4.6mm x 33mm. The stationary phase particle size is 3m.

Solvents

A : Aqueous solvent = 10mMol Ammonium Acetate + 0.1% Formic Acid
B : Organic solvent = 95 %Acetonitrile + 0.05% Formic Acid

Method

The generic method used has 5.5 minute runtime, which comprises of a 4.7-minute gradient (0-100% B) followed by a 0.6 minute column flush and 0.2 minute re-equilibration step.

Flow rate

The above method has a flow rate of 3ml/mins

Conditions used for NMR

Hardware

Bruker 400MHz Ultrashield
Bruker B-ACS60 Autosampler
Bruker Advance 400 Console

Software

User interface – NMR Kiosk
Controlling software – XWin NMR version 3.0

Conditions used for the Biotage Horizon.

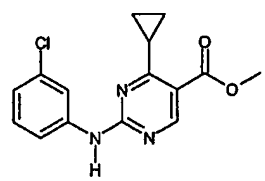
Column: Biotage C18HS 25+S
Fraction volume: 9ml UV Threshold : 0.03AU
Solvent A= Water , B= Acetonitrile
Gradient :

Volume(ml)	A	B
0	70%	30%
240	0%	100%

Abbreviations:

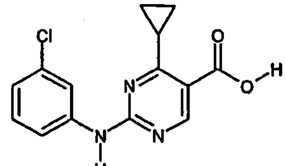
AcOH (acetic acid), Bn (benzyl), Bu, Pr, Me, Et (butyl, propyl, methyl ethyl), DMSO (dimethyl sulfoxide), DCM (dichloromethane), DME (1,2-dimethoxyethane), DMF (N,N-dimethylformamide), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), EtOAc (ethyl acetate), EtOH (ethanol), HPLC (High pressure liquid chromatography), LC/MS (Liquid chromatography/Mass spectroscopy), MDAP (Mass Directed AutoPurification), MeCN (acetonitrile), MeOH (methanol), NMR (Nuclear Magnetic Resonance (spectrum)), NMP (n-methyl pyrrolidone), SPE (Solid Phase Extraction), THF (tetrahydrofuran), s, d, t, q, m, br (singlet, doublet, triplet, quartet, multiplet, broad.)

Intermediate 1: 2-(3-Chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carboxylic acid methyl ester



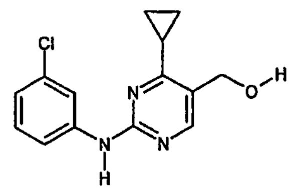
A solution of N-(3-chloro-phenyl)-guanidine nitrate salt (prepared as in WO 95/09851, 5.00g, 0.0215mol. 1eq) in ethanol (100ml) was stirred with sodium ethoxide (1.48g, 0.0217mol, 1.01eq) for 2 min. (1-Cyclopropyl-methanoyl)-dimethylamino-acrylic acid methyl ester (prepared as in EP1101763A2, 4.24g, 0.0215mol, 1eq) was added, and the reaction mixture was heated at 92^{o} for 2 hours. The volatiles were removed *in vacuo* and the concentrated reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, brine, dried ($MgSO_4$), filtered, and the volatiles were removed *in vacuo*. The residue was then purified by chromatography using Biotage Flash 40M cartridge eluting with 10% EtOAc:*iso*-hexane, increasing to 30% EtOAc:*iso*-hexane, to yield the title compound (4.14g, 0.0136mol, 63%) as an off-white solid.
LC/MS t=3.73 min. Molecular ion observed [MH+] 304, consistent with molecular formula $C_{15}H_{14}{}^{35}ClN_3O_2$

Intermediate 2: 2-(3-Chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carboxylic acid



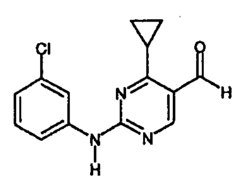
2-(3-Chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carboxylic acid methyl ester (2.23g, 0.735mmol, 1eq), was dissolved in THF (20ml) and lithium hydroxide (0.926g, 0.022mol, 3eq), was added. The reaction mixture was stirred at 21°C for 48 hours. The volatiles were removed *in vacuo* and water added. The mixture was acidified to pH1 with conc hydrochloric acid, stirred for 2 min, the precipitate was filtered off, and washed with water. The solid was then co-evaporated with toluene to yield the dry title compound (1.00g, 0.345mmol, 47%) as a white solid.
LC/MS t=3.77 min. Molecular ion observed [MH+] 290, consistent with molecular formula $C_{14}H_{12}{}^{35}ClN_3O_2$

Intermediate 3: [2-(3-Chloro-phenylamino)-4-cyclopropyl-pyrimidin-5-yl]-methanol



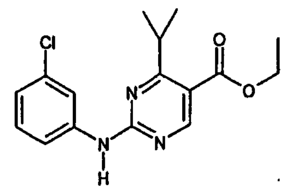
N-methylmorpholine (0.559ml, 0.497mmol, 1eq) and isobutylchloroformate (0.648ml, 0.497mmol, 1eq) were successively added to a stirred solution of 2-(3-chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carboxylic acid (1.441g, 0.497mmol, 1eq) in 1,2-dimethoxyethane (25ml) at −15°C and stirring was continued for 10 min at −15°C. The precipitate was filtered off, discarded, and a solution of $NaBH_4$ (0.284g, 0.747mmol, 1.5eq) in water (1.5ml) was added at 0°C. The reaction mixture was stirred for 3 min, quenched with water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield the title compound (0.895g, 0.325mmol, 65%) as a yellow oil.
LC/MS t=3.22 min. Molecular ion observed [MH+] 276, consistent with molecular formula $C_{14}H_{14}{}^{35}ClN_3O$

Intermediate 4: 2-(3-Chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carbaldehyde



Manganese(IV)oxide (2.757g, 0.032mol, 10eq) and sodium chloride (3.79g, 0.044mol, 4eq) were added to a stirred solution of 2-(3-chloro-phenylamino)-4-cyclopropyl-pyrimidin-5-yl]-methanol (0.923g, 0.317mmol, 1eq) in dichloromethane (40ml). After stirring at 21°C for 18 hours, the precipitate was filtered off, washed with dichloromethane, and dried in vacuo to yield the title compound (0.150g, 0.055mmol, 17%) as a pale yellow solid.
LC/MS t=3.56 min. Molecular ion observed [MH+] 274, consistent with molecular formula $C_{14}H_{12}{}^{35}ClN_3O$.

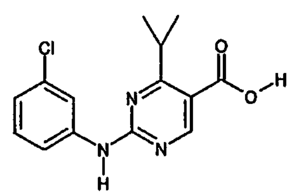
Intermediate 5: 2-(3-Chloro-phenylamino)-4-isopropyl-pyrimidine-5-carboxylic acid ethyl ester



The title compound was prepared as for Intermediate 1 using 1-(isopropyl-methanoyl)-dimethylamino-acrylic acid ethyl ester (prepared in a manner similar to that described by G Mennozi, J Heterocyclic Chem, 1987, 24, 1669)

LC/MS t=3.73 [MH+] 304 Consistent with molecular formula $C_{16}H_{18}Cl^{35}N_3O_2$

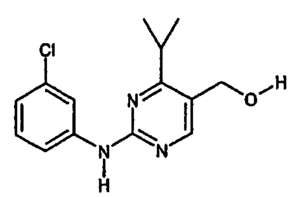
Intermediate 6: 2-(3-Chloro-phenylamino)-4-isopropyl-pyrimidine-5-carboxylic acid



The title compound was prepared as for Intermediate 2 using 2-(3-chloro-phenylamino)-4-isopropyl-pyrimidine-5-carboxylic acid ethyl ester.

LC/MS t=3.81 min. Molecular ion observed [MH+] 320, consistent with molecular formula $C_{14}H_{14}{}^{35}ClN_3O_2$

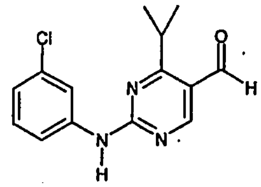
Intermediate 7: [2-(3-Chloro-phenylamino)-4-isopropyl-pyrimidin-5-yl]-methanol



The title compound was prepared from 2-(3-chloro-phenylamino)-4-isopropyl-pyrimidine-5-carboxylic acid using the procedure described Intermediate 3.

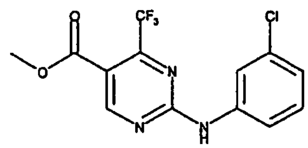
LC/MS t=3.28 min. Molecular ion observed [MH+] 278, consistent with molecular formula $C_{14}H_{16}{}^{35}ClN3O$.

Intermediate 8: 2-(3-Chloro-phenylamino)-4-isopropyl-pyrimidine-5-carbaldehyde



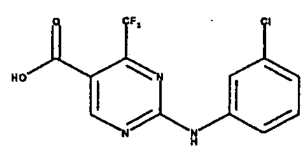
The title compound was prepared from [2-(3-chloro-phenylamino)-4-isopropyl-pyrimidin-5-yl]-methanol using the procedure described for Intermediate 4.
LC/MS t=3.62 min. Molecular ion observed [MH+] 276, consistent with molecular formula $C_{14}H_{14}{}^{35}ClN_3O$

Intermediate 9: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl ester



To a solution of methyl 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylate (11.0 g, ex Maybridge) in 1,4-dioxan (30 ml) was added 3-chloroaniline (17 g) and the solution stirred under reflux for 2 h. 1,4-Dioxan was removed under reduced pressure and the residue stirred in 2N hydrochloric acid (150 ml) for 1h. The solid was filtered onto a sinter and washed with 2N hydrochloric acid (2 x 100 ml) and water (5 x 100 ml). The solid was transferred to a crystallising dish and dried at 50°C over sodium hyroxide in a vacuum oven (15.2 g)
NMR (DMSO-d6) δ 3.86 (3H, s), 7.15 (1H, dd), 7.39 (1H, t), 7.67 (1H, dd), 7.97 (1H, s), 9.10 (1H, s), 10.95 (1H, s).
LC/MS, t = 3.69 min, molecular ion observed [MH+] 332, consistent with $C_{13}H_9ClF_3N_3O_2$.

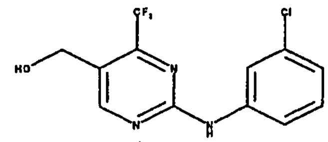
Intermediate 10: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid



To a suspension of 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl ester, (15.2 g) in methanol (100 ml) was added a solution of potassium hydroxide (7.68 g) in methanol (100 ml) and the mixture stirred at reflux for 3 h. Methanol was removed under reduced pressure and water (200 ml) added. The solution was washed with ether and concentrated hydrochloric acid was added to adjust the acidity to pH 1. The acidified aqueous was extracted with ethyl acetate (2 x 200 ml) and the combined extract was washed with water (3 x 200 ml). The dried ($MgSO_4$) organic layer was evaporated and the residue triturated with isohexane to afford 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (14.35 g).
NMR (DMSO-d6) δ 7.52 (1H, dd), 7.78 (1H, t), 8.07 (1H, dd), 8.38 (1H, s), 9.49 (1H, s), 11.20 (1H, s), 14.50 (1H, s).

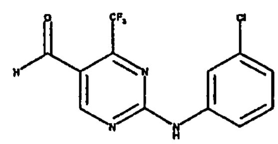
LC/MS, t = 3.83 min, molecular ion observed [MH^+] 318, consistent with $C_{12}H_7ClF_3N_3O_2$.

Intermediate 11: [2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol



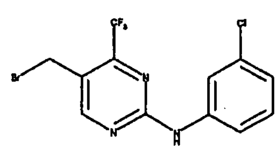
To a solution of 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (3.0 g) in 1,2-dimethoxyethane (48 ml) under nitrogen at –15°C was added N-methylmorpholine (1.05 ml) followed by isobutyl chloroformate (1.22 ml). After 10 minutes, the precipitated N-methylmorpholine hydrochloride was removed by filtration and the filtrate, under nitrogen, was treated with a solution of sodium borohydride (537 mg) in water (5 ml). After a further 5 minutes, the reaction was quenched by the addition of water. The aqueous mixture was extracted with ethyl acetate (3 x 150ml), combined, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by Biotage flash chromatography over Merck 9385 silica gel eluting with 3:2 isohexane : ethyl acetate to afford [2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol (1.97 g).
NMR (DMSO-d6) δ 4.57 (2H, d), 5.45 (1H, s), 7.04 (1H, dd), 7.33 (1H, t), 7.66 (1H, dd), 7.97 (1H, t), 8.84 (1H, s), 10.30 (1H, s).
LC/MS, t = 3.26 min, molecular ion observed [MH^+] 304, consistent with $C_{12}H_9ClF_3N_3O$.

Intermediate 12: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde



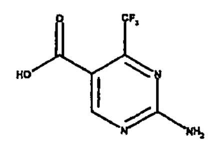
To a solution of [2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol Intermediate 11 (1.97 g) in dichloromethane (81 ml) was added sodium chloride (5.39 g) and manganese (IV) oxide (5.64 g), and the mixture stirred at room temperature overnight. The mixture was filtered onto a bed of Celite washing with dichloromethane. The combined filtrates were evaporated under reduced pressure to afford 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde (1.76 g).
NMR (DMSO-d6) δ 7.20 (1H, dd), 7.41 (1H, t), 7.69 (1H, dd), 7.99 (1H, s), 9.18 (1H, s), 10.00 (1H, s), 11.10 (1H, s).
LC/MS, t = 3.60 min, molecular ion observed [MH^+] 302, consistent with $C_{12}H_7ClF_3N_3O$

Intermediate 13: (5-Bromomethyl-4-trifluoromethyl-pyrimidin-2-yl)-(3-chloro-phenyl)-amine



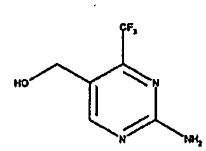
To a solution of [2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol (42 mg), and carbon tetrabromide (183 mg) in tetrahydrofuran (2 ml) was added triphenylphosphine (72 mg). The solution was stirred at room temperature for 1h and then evaporated under reduced pressure. The residue was dissolved in isohexane:dichloromethane 3:1 and purified by chromatography on a Sep-pak cartridge of silica gel, eluting with isohexane:dichloromethane 2:1 to afford the title compound as a pale yellow solid (27 mg).
NMR (DMSO-d6) δ 4.77 (2H, s), 7.08 (1H, dd), 7.36 (1H, t), 7.65 (1H, dd), 7.95 (1H, s), 8.94 (1H, s), 10.60 (1H, s).
LC/MS, t = 3.89 min, molecular ion observed [MH^+] 368, consistent with $C_{12}H_8{}^{81}Br^{35}ClF_3N_3$.

Intermediate 14 . 2-Amino-4-trifluoromethyl-pyrimidine-5-carboxylic acid



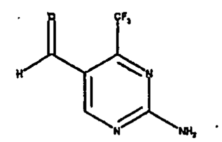
A solution of 2-amino-4-trifluoromethyl-pyrimidine-5-carboxylic acid ethyl ester (commercially available from Maybridge) (14.9 g) in methanol (300 ml) containing potassium hydroxide (10.65 g) was refluxed for 4h. The solvent was removed under reduced pressure and the residue dissolved in water (150 ml). The aqueous was washed with diethyl ether (75 ml) and then acidified to pH 1 with concentrated hydrochloric acid to afford a white precipitate. The solid was filtered off, washed with water and dried to afford the title compound (12.76 g).
NMR (DMSO-d6) δ 7.94 (2H, s), 8.82 (1H, s), 13.30 (1H, s).
LC/MS, t = 1.10 min, molecular ion observed [MH^+] 208, consistent with $C_6H_4F_3N_3O_2$.

Intermediate 15. (2-Amino-4-trifluoromethyl-pyrimidin-5-yl)-methanol



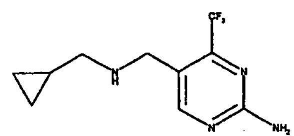
To a solution of 2-amino-4-trifluoromethyl-pyrimidine-5-carboxylic acid (4.35 g) in 1,2-dimethoxyethane (200 ml) at –12°C was added N-methylmorpholine (2.30 ml) followed by isobutyl chloroformate (2.72 ml). After 5 minutes, the precipitated N-methylmorpholine hydrochloride was removed by filtration and the filtrate treated with a solution of sodium borohydride (1.2 g) in water (10 ml). After a further 30 minutes, the reaction was quenched by the addition of water. The aqueous mixture was extracted with ethyl acetate (3 x 150ml), and the combined, dried ($MgSO_4$) organic extracts were evaporated in vacuo. The residue was purified by Biotage flash chromatography over Merck 9385 silica gel eluting with 1:1 isohexane : ethyl acetate to afford the title compound (1.2g).
NMR (DMSO-d6) δ 4.45 (2H, d), 5.25 (1H, t), 7.19 (2H, s), 8.52 (1H, s).
LC/MS, t = 1.40 min, molecular ion observed [MH^+] 194, consistent with $C_6H_6F_3N_3O$.

Intermediate 16 : 2-Amino-4-trifluoromethyl-pyrimidine-5-carbaldehyde



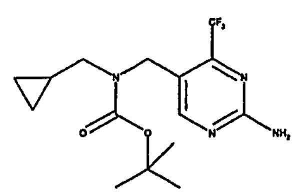
To a solution of (2-amino-4-trifluoromethyl-pyrimidin-5-yl)-methanol (1.2 g) in ethyl acetate (20 ml) was added sodium chloride (5.09 g) and manganese (IV) oxide (5.4 g), and the mixture stirred at room temperature overnight. The mixture was filtered onto a bed of Celite washing with ethyl acetate. The solvent was removed under reduced pressure to afford the title compound (1.16 g).
NMR (DMSO-d6) δ 8.38 (2H, d), 8.92 (1H, s), 9.94 (1H, s).
LC/MS, t = 1.80 min, molcelar ion observed [M-H$^+$] 190, consistent with molecular formula $C_6H_4F_3N_3O$.

Intermediate 17: 5-[(Cyclopropylmethyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-ylamine



A mixture of 2-amino-4-trifluoromethyl-pyrimidine-5-carbaldehyde (1.16 g), powdered 4A molecular sieves, cyclopropylmethylamine (518 mg) and glacial acetic acid (348 ul) in tetrahydrofuran (20 ml) was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (1.8 g) was added and the mixture stirred overnight. The mixture was diluted with ethyl acetate and washed with 1N NaOH and brine then dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a pale yellow solid (1.35 g).
NMR (DMSO-d6) δ 0.09 (2H, m), 0.38 (2H, m), 0.85 (1H, m), 2.39 (2H, d), 3.68 (2H, s), 7.15 (2H, s), 8.56 (1H, s).
LC/MS, t = 1.20 min, molecular ion observed [MH$^+$] 247, consistent with molecular formula $C_{10}H_{13}F_3N_4$.

Intermediate 18: (2-Amino-4-trifluoromethyl-pyrimidin-5-ylmethyl)-cyclopropylmethyl-carbamic acid dimethyl-ethyl ester



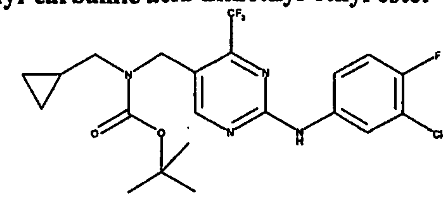
To a solution of 5-[(cyclopropylmethyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-ylamine (1.35 g) in ethyl acetate (20 ml), was added triethylamine (0.916 ml) followed by di-tert-butyl dicarbonate (1.31 g) and the solution stirred at room temperature for 3h. This was diluted with ethyl acetate, washed with water, and the dried ($MgSO_4$) organic layer was evaporated under reduced

pressure. The residue was triturated with hexane to afford the title compound as a white solid (1.56 g).

NMR (DMSO-d6) δ 0.12 (2H, d), 0.38 (2H, m), 0.93 (1H, m), 1.38 (9H, m), 3.08 (2H, s), 4.44 (2H, s), 7.22 (2H, s), 8.29 (1H, s).

LC/MS, t = 3.37 min, [M-^{t}Bu^{+}] 291.

Intermediate 19: [2-(3-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-cyclopropylmethyl-carbamic acid dimethyl-ethyl ester



A mixture of (2-amino-4-trifluoromethyl-pyrimidin-5-ylmethyl)-cyclopropylmethyl-carbamic acid dimethyl-ethyl ester, (100 mg), 4-bromo-2-chloro-1-fluorobenzene (60 mg), cesium carbonate (131 mg), tris(dibenzylideneacetone)dipalladium (0) (3 mg) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (2mg) and 1,4-dioxan (1 ml) was heated to 100°C under nitrogen for 24h. A mixture of tris(dibenzylideneacetone)dipalladium (0) (3 mg) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (2mg) was added 3 times at two hour intervals, and the reaction allowed to cool. The mixture was diluted with ethyl acetate, washed with water,dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified using the MDAP system detailed at the beginning of the experimental section to afford the title compound as a yellow solid (63 mg).

NMR (DMSO-d6) δ 0.15 (2H, d), 0.40 (2H, m), 0.97 (1H, m), 1.32 (9H, m), 3.15 (2H, s), 4.55 (2H, s), 7.39 (1H, t), 7.67 (1H, m), 8.05 (1H, m), 8.58 (1H, s), 10.40 (1H, s).

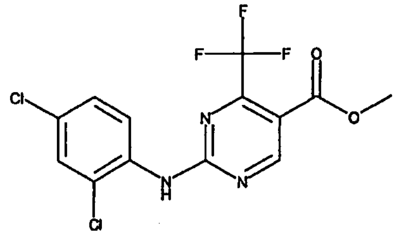
LC/MS, t = 4.50 min, molecular ion observed [M+H^{+}] 475, consistent with $C_{21}H_{23}F_4ClN_4O_2$.

Intermediate 20: 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid

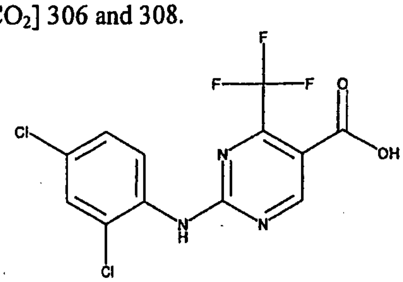
(a). To a solution of methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (0.5 g, ex Maybridge) in 1,4-dioxan (5 ml) was added 2,4-dichloroaniline (1.7 g) and the solution stirred at reflux temperature for 24 h. 1,4-Dioxan was removed under reduced pressure and ethyl acetate (15 ml) added. The solution was washed sequentially with 2N hydrochloric acid (10 ml) and water (3 x 10 ml), dried ($MgSO_4$), evaporated and triturated with hexane to afford methyl 2-(2,4-dichlorophenyl-amino)-4-trifluoromethyl-pyrimidine-5-carboxylate (214 mg).

NMR (400MHz, $CDCl_3$) δ 3.95 (3H, s), 7.33 (1H, d), 7.46 (1H, d), 7.99 (1H, s), 8.48 (1H, d), 9.06 (1H, s).

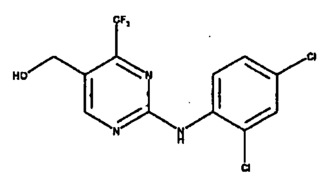
LC/MS, t = 3.74 min, [MH^{+}] 366 and 368.



(b). To a solution of methyl 2-(2,4-dichlorophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylate (0.21 g) in ethanol (15 ml) was added a solution of potassium hydroxide (205 mg) in ethanol (10 ml) and the solution stirred at reflux for 15 h. Ethanol was removed under reduced pressure and water (15 ml) added. The solution was washed with ether and concentrated hydrochloric acid added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with water and dried in vacuo at 50°C to afford 2-(2,4-dichlorophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (0.18 g).
NMR (400MHz, DMSO-d6) δ 7.47 (1H, d), 7.60 (1H, d), 7.75 (1H, s), 8.96 (1H, s), 10.3 (1H, s), 13.6 (1H, s).
LC/MS, t = 4.17 min, [MH^+-CO_2] 306 and 308.

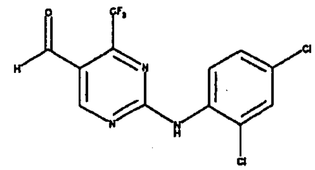


Intermediate 21: [2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol



To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (3.0 g), in 1,2-dimethoxyethane (53 ml) at –20°C was added N-methylmorpholine (1.09 ml) followed by isobutyl chloroformate (1.38 ml). After 10 minutes, the precipitated N-ethylmorpholine hydrochloride was removed by filtration and the filtrate treated at –20°C with a solution of sodium borohydride (540 mg) in water (15 ml). After a further 5 minutes, the reaction was quenched by the addition of water. The aqueous mixture was extracted with ethyl acetate (3 x 150ml), and the combined, dried ($MgSO_4$) organic extracts were evaporated. The residue was purified by Biotage Horizon chromatography eluting with 5-50% ethyl acetate : isohexane to afford the title compound (0.69 g).
NMR (DMSO-d6) δ 4.54 (2H, d), 5.42 (1H, t), 7.44 (1H, dd), 7.64 (1H, d), 7.68 (1H, d), 8.71 (1H, s), 9.63 (1H, s).
LC/MS, t = 3.57 min, molecular ion observed [MH^+] 338, consistent with $C_{12}H_8Cl_2F_3N_3O$.

Intermediate 22: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde



To a solution of [2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol, (0.69 g) in dichloromethane (25 ml) was added sodium chloride (1.67 g) and manganese (IV) oxide (1.77 g), and the mixture stirred at room temperature for 48h. The mixture was filtered onto a bed of Celite washing with dichloromethane. The filtrate was evaporated under reduced pressure to afford the title compound (0.6 g).

NMR (DMSO-d6) δ 7.50 (1H, dd), 7.58 (1H, d), 7.75 (1H, d), 9.05 (1H, s), 10.00 (1H, s), 10.75 (1H, s).

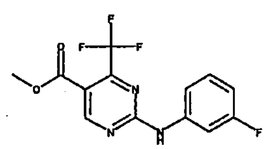
LC/MS, t = 3.62 min, molecular ion observed [MH$^+$] 336, consistent with $C_{12}H_6Cl_2F_3N_3O$.

Intermediate 23: 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid

(a). In a manner similar to Intermediate 9, methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (0.5 g) and 3-fluoroaniline (1.16 g) afforded methyl 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylate (0.65 g).

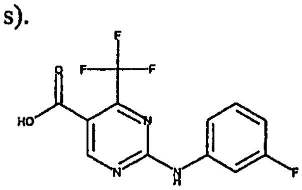
NMR (400MHz, DMSO-d6) δ 3.88 (3H, s), 6.95 (1H, t of d), 7.40 (1H, q), 7.54 (1H, d), 7.79 (1H, d of t), 9.12 (1H, s), 10.95 (1H, s).

LC/MS, t = 3.50 min, [MH$^+$] 316.

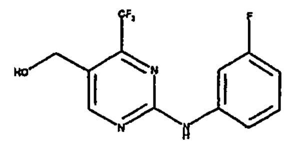


(b). In a manner similar to Intermediate 10, methyl 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (0.65g) afforded 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (0.54 g).

NMR (400MHz, DMSO-d6) δ 6.90 (1H, t of d), 7.39 (1H, q), 7.55 (1H, d), 7.80 (1H, d of t), 9.10 (1H, s), 10.85 (1H, s), 13.7 (1H, br s).

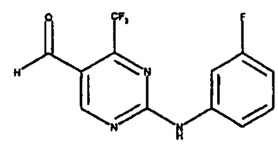


Intermediate 24: [2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol



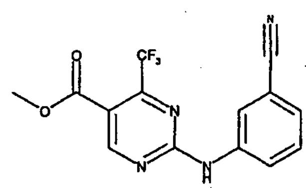
Prepared and purified in a similar manner to [2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol (Intermediate 21), using 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid to afford the title compound (1.98 g).
NMR (DMSO-d6) δ 4.57 (2H, d), 5.48 (1H, s), 6.85 (1H, m), 7.33 (1H, q), 7.50 (1H, dd), 7.79 (1H, dt), 8.85 (1H, s), 10.40 (1H, s).
LC/MS, t = 3.20 min, molecular ion observed [MH^+] 288, consistent with $C_{12}H_9F_4N_3O$

Intermediate 25: 2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde



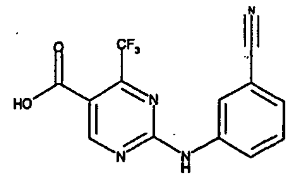
Prepared and purified in a similar manner to 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde (Intermediate 12), using [2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol, to afford the title compound (1.78g).
NMR (DMSO-d6) δ 6.97 (1H, m), 7.42 (1H, q), 7.56 (1H, dd), 7.79 (1H, dd), 9.18 (1H, s), 10.07 (1H, s), 11.17 (1H, s).
LC/MS, t = 3.42 min, molecular ion observed [MH^+] 286, consistent with $C_{12}H_7F_4N_3O$.

Intermediate 26: 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl ester



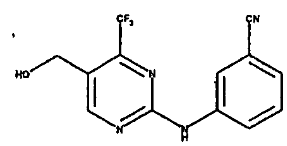
To a solution of methyl 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylate (4.0 g, ex Maybridge) in 1,4-dioxan (20 ml) was added 3-cyanoaniline (5.88 g) and the solution stirred under reflux for 3 h. 1,4-Dioxan was removed under reduced pressure and the residue stirred in 2N hydrochloric acid (100 ml) for 2h. The solid was filtered onto a sinter, washed with 2N hydrochloric acid (2 x 50 ml), water (5 x 50 ml) and then sucked dry.
LC/MS, t = 3.38 min, molecular ion observed [MH^+] 323, consistent with $C_{14}H_9F_3N_4O_2$.

Intermediate 27: 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid



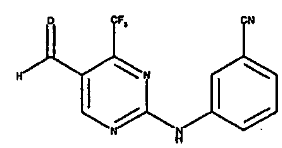
To a solution of 2-(3-cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl ester, in tetrahydrofuran (40 ml) was added a solution of lithium hydroxide monohydrate (2.09 g) in water (13 ml) and the mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and water added. The solution was washed with ether and concentrated hydrochloric acid was added to adjust the acidity to pH 1. The precipitate was filtered onto a sinter and washed with water until neutral to afford the title compound (4.68 g).
NMR (DMSO-d6) δ 7.56 (2H, m), 8.00 (1H, d), 8.27 (1H, s), 9.11 (1H, s), 10.95 (1H, s), 13.70 (1H, s).
LC/MS, t = 3.32 min, molecular ion observed [MH$^+$] 309, consistent with $C_{14}H_9F_3N_4O_2$.

Intermediate 28: [2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol



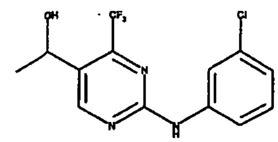
Prepared and purified in a similar manner to [2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol (Intermediate 11), using 2-(3-cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid, to afford the title compound (2.41g).
NMR (DMSO-d6) δ 4.58 (2H, d), 5.50 (1H, t), 7.45 (1H, d), 7.54 (1H, t), 7.99 (1H, dd), 8.01 (1H, s), 8.88 (1H, s), 10.40 (1H, s).
LC/MS, t = 3.04 min, molecular ion observed [MH$^+$] 295, consistent with $C_{13}H_9F_3N_4O$.

Intermediate 29: 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde



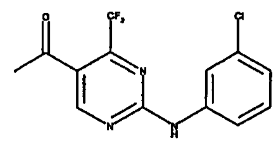
Prepared and purified in a similar manner to 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde (Intermediate 12), using [2-(3-cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanol, to afford the title compound (2.22g).
NMR (DMSO-d6) δ 7.61 (2H, m), 8.03 (1H, dd), 8.28 (1H, S), 9.20 (1H, s), 10.10 (1H, s), 11.30 (1H, s).
LC/MS, t = 3.26 min, molecular ion observed [MH$^+$] 293, consistent with $C_{13}H_7F_3N_4O$.

Intermediate 30: 1-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanol



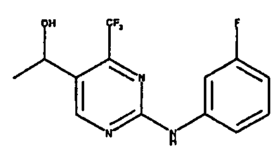
To a solution of 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde, (1.15 g) in tetrahydrofuran (25 ml) at –78^{O}C under nitrogen was added methylmagnesium bromide (3.0M in diethyl ether, 3.43 ml) dropwise. After 1h, the reaction was quenched by the addition of saturated ammonium chloride (50 ml). and allowed to warm to room temperature. The aqueous was extracted with dichloromethane (2 x 40 ml) and the combined dried (Na_2SO_4) organic extracts were evaporated in vacuo. The residue was purified by Biotage flash chromatography over Merck 9385 silica gel eluting with 4:1 isohexane:ethyl acetate to afford the title compound (1.1 g).
NMR (DMSO) δ 1.40 (3H, d), 5.00 (1H, t), 5.60 (1H, d), 7.05 (1H,dd), 7.33 (1H, t), 7.66 (1H, dd), 7.97 (1H, t), 9.00 (1H, s), 10.35 (1H, s).
LC/MS, t = 3.59 min, molecular ion observed [MH^+] 318, consistent with $C_{13}H_{11}ClF_3N_3O$.

Intermediate 31: 1-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanone



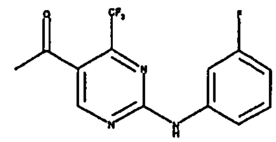
To a solution of 1-[2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanol, (1.1 g) in dichloromethane (30 ml) was added sodium chloride (2.83 g) and manganese (IV) oxide (3.0 g), and the mixture stirred at room temperature for 72h. The mixture was then heated under reflux overnight. The mixture was filtered onto a bed of Celite washing with dichloromethane. The filtrate was evaporated under reduced pressure to afford the title compound (520 mg).
NMR (DMSO) δ 2.60 (3H, s), 7.13 (1H,dd), 7.38 (1H, t), 7.70 (1H, dd), 8.03 (1H, t), 9.50 (1H, s), 10.85 (1H, s).
LC/MS, t = 3.62 min, [MH^+] 316.

Intermediate 32: 1-[2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanol



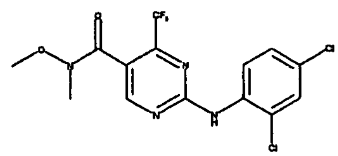
Prepared and purified in a similar manner to 1-[2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanol (Intermediate 30), using 2-(3-fluorohenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde, to afford the title compound (0.99 g).
NMR (DMSO) δ 1.40 (3H, d), 5.00 (1H, t), 5.60 (1H, d), 6.80 (1H, m), 7.35 (1H, t), 7.50 (1H, dd), 7.80 (1H, dt), 9.00 (1H, s), 10.40 (1H, s). LC/MS, t = 3.37 min, molecular ion observed [MH^+] 302, consistent with $C_{13}H_{11}F_4N_3O$.

Intermediate 33: 1-[2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanone



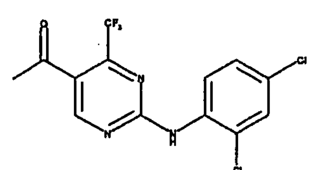
Prepared and purified in a similar manner to 1-[2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanone (Intermediate 31), using 1-[2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanol, to afford the title compound (0.58 g).
NMR (DMSO) δ 2.60 (3H, s), 7.20 (1H, m), 7.38 (1H, q), 7.50 (1H, dd), 7.80 (1H, dt), 9.25 (1H, s), 10.85 (1H, s).
LC/MS, t = 3.42 min, molecular ion observed [MH^+] 300, consistent with $C_{13}H_9F_4N_3O$.

Intermediate 34: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methoxy-methyl-amide



To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid, (3.0 g) in dimethylformamide (30 ml) was added N-ethyl morpholine (2.94 g), 1-hydroxybenzotriazole hydrate (1.799 g), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (2.94 g) and N,O-dimethylhydroxylamine hydrochloride (0.99 g). The solution was stirred for 3 h and allowed to stand overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (50 ml) added. The solution was washed sequentially with 5% sodium bicarbonate solution (50 ml), water (50 ml), 5% citric acid solution (50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated to afford the title compound (3.13 g).
NMR (DMSO) δ 3.25 (3H, s), 3.49 (3H, s), 7.46 (1H, d), 7.61 (1H, d), 7.72 (1H, d), 8.76 (1H, s), 10.10 (1H, s).
LC/MS, t = 3.50 min, molecular ion observed [MH^+] 395, consistent with $C_{14}H_{11}Cl_2F_3N_4O$.

Intermediate 35: 1-[2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanone

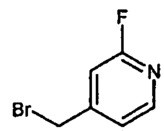


To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methoxy-methyl-amide, (0.5 g), in dry tetrahydrofuran (10 ml) at –10°C under nitrogen was added dropwise methyl lithium (1.6M in diethyl ether, 1.58 ml) and the solution stirred at 0 °C for 3h. Further methyl lithium (1.6M in diethyl ether, 1.58 ml) was added at –10°C dropwise and after 10 minutes the reaction was quenched by the addition of aqueous saturated ammonium chloride. The

reaction was allowed to warm to room temperature, and the aqueous was extracted with ethyl acetate. The combined dried (Na_2SO_4) organic extracts were evaporated, and the residue purified by Biotage flash chromatography over Merck 9385 silica gel eluting with 7:3 isohexane : ethyl acetate to afford the title compound (0.11 g).
NMR (DMSO) δ 2.56 (3H, s), 7.57 (1H,dd), 7.73 (1H, d), 7.75 (1H, d), 9.07 (1H, s), 10.35 (1H, s).
LC/MS, t = 3.63 min, molecular ion observed [MH^+] 350, consistent with $C_{13}H_8Cl_2F_3N_3O$.

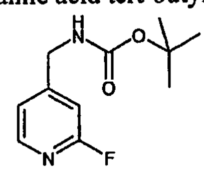
Intermediate 36: C-(2-Fluoro-pyridin-4-yl)-methylamine dihydrochloride

(a). 4-Bromomethyl-2-fluoro-pyridine.



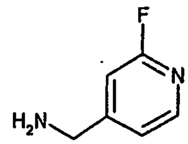
To a solution of 2-fluoro-4-methylpyridine (1.0 g, ex Lancaster) in carbon tetrachloride (10 ml) was added N-bromosuccinimide (1.6 g, ex Lancaster) and 1,1'- azobis (cyclohexanecarbonitrile) (100 mg, ex Aldrich). The mixture was then refluxed for 24h. Carbon tetrachloride was removed under reduced pressure and the crude oily solid was used in the next stage without purification.
LC/MS, t = 2.38 min, [MH^+] 190 consistent with $C_6H_5{}^{79}BrFN$.

(b). (2-Fluoro-pyridin-4-ylmethyl)-carbamic acid tert-butyl ester.



To crude 4-bromomethyl-2-fluoro-pyridine in an ice bath was added 25% ammonia solution (10 ml, ex BDH) and the mixture stirred at 0° for 5h. Ammonia solution was removed under reduced pressure and the yellow oily solid residue dissolved in dichloromethane (10 ml) and dimethylformamide (1 ml). The solution was cooled in an ice bath and triethylamine (1.5 ml, ex BDH) was added followed by di-tert-butyl dicarbonate (1.0 g, ex Avocado). The solution was stirred at 0° for 1h and then the dichloromethane removed under reduced pressure. The residue was dissolved in ethyl acetate and washed twice with water, dried ($MgSO_4$) and evaporated to give a yellow oil. This was purified by Biotage chromatography (100 g, silica column) eluting with 30% ethyl acetate in hexane to afford the title compound as a white solid (358 mg).
NMR (400MHz, DMSO-d6) δ 1.40 (9H, s), 4.20 (2H, d), 6.97 (1H, s), 7.20 (1H, d), 7.60 (1H, t), 8.17 (1H, d)
LC/MS, t = 2.60 min, $[M - Me2C{=}CH2 + H]^+$ 171, consistent with $C_{11}H_{15}FN_2O_2$

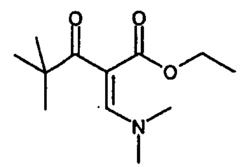
(c). C-(2-Fluoro-pyridin-4-yl)-methylamine dihydrochloride.



dihydrochloride

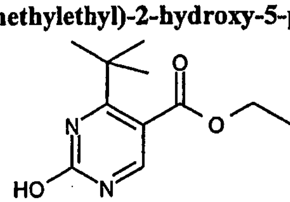
(2-Fluoro-pyridin-4-ylmethyl)-carbamic acid tert-butyl ester (350mg) was treated at room temperature with 4N hydrochloric acid in 1,4-dioxan (5 ml) and stirred for 2h. The white precipitate was filtered, washed with fresh ether and dried to afford the title compound (200 mg). NMR (400MHz, DMSO-d6) δ 4.14 (2H, d), 7.38 (1H, s), 7.51 (1H, d), 8.28 (1H, d), 8.82 (3H, s).

Intermediate 37: 2-Dimethylaminomethylene-4,4-dimethyl-3-oxo-pentanoic acid ethyl ester



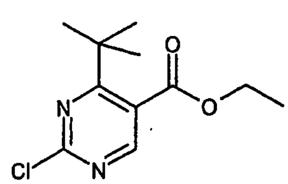
Ethyl pivaloylacetate (Ex Avacado) (99.6g) and N,N-dimethylformamide dimethyl acetal (172g) were heated with stirring at 100°C for 4 hours. The reaction mixture was allowed to cool and the volatiles removed in vacuo. The residue was washed with aqueous 1M NaOH and the organic layer washed with brine, dried ($MgSO_4$), and the volatiles were removed in vacuo to yield the title compound as an orange oil (131g).
NMR (d^6-DMSO) δ 0.95-1.20 (12H, m), 2.83 (6H, brs), 3.95-4.10 (2H, m), 7.30 (1H, s).

Intermediate 38: Ethyl 4-(1,1-dimethylethyl)-2-hydroxy-5-pyrimidinecarboxylate



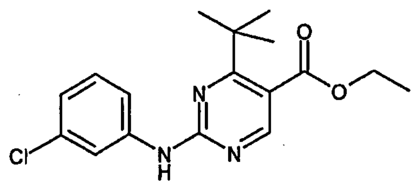
2-Dimethylaminomethylene-4,4-dimethyl-3-oxo-pentanoic acid ethyl ester (71.5g) and urea (20.79g) were heated at 155°C in glacial acetic acid (300ml) for 16 hours. The volatiles were removed in vacuo and the residue co-evaporated twice with toluene. The residue was triturated with iso-hexane and filtered off to yield the title compound as a yellow crystalline solid (17.2g).
NMR (d^6-DMSO) δ 1.23-1.35 (12H, m), 4.22 (2H, q), 8.23 (1H, s), 12.20 (1H, brs).
LC/MS t= 2.15 min [MH^+]= 225 consistent with molecular formula $C_{11}H_{16}N_2O_3$

Intermediate 39: Ethyl 2-chloro-4-(1,1-dimethylethyl)-5-pyrimidinecarboxylate



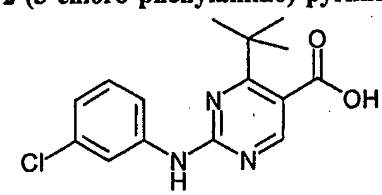
Ethyl 4-(1,1-dimethylethyl)-2-hydroxy-5-pyrimidinecarboxylate (15.56g) was suspended in phenyldichlorophosphate (150ml) and was stirred at 180°C for 2 hours. The reaction mixture was poured onto ice (excess) and the mixture was basified to pH 7 using solid $NaHCO_3$. The reaction mixture was dissolved in EtOAc and washed with water. The organic layer was washed with brine, dried ($MgSO_4$) and the volatiles were removed in vacuo to yield the title compound as a brown liquid (12.5g).
NMR (d^6-DMSO) δ 1.26-1.40 (12H, m), 4.37 (2H, q), 8.85 (1H, s).
LC/MS t= 3.26 min [MH^+]= 243 consistent with molecular formula $C_{11}H_{15}{}^{35}ClN_2O_2$

Intermediate 40: 4-*tert*-Butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carboxylic acid ethyl ester



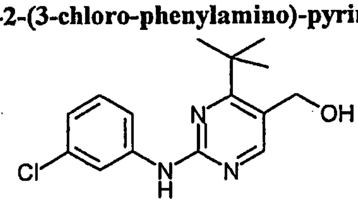
3-Chloroaniline (4.00ml) was added to a solution of ethyl 2-chloro-4-(1,1-dimethylethyl)-5-pyrimidinecarboxylate (3.00g) in dioxan (10ml) and the solution stirred at 100°C for 3 hours. The volatiles were removed in vacuo and the residue dissolved in EtOAc and washed three times with aqueous 2M HCl. The organic layer was then washed with brine, dried ($MgSO_4$), and the volatiles were removed in vacuo to yield the title compound as a brown oil which solidified (3.99g).
NMR (d^6-DMSO) δ 1.32 (3H, t), 1.39 (9H, s), 4.30 (2H, q), 7.05 (1H, d), 7.33 (1H, t), 7.61 (1H, d), 8.01 (1H, s), 8.60 (1H, s).
LC/MS t= 4.22 min [MH^+]= 334 consistent with molecular formula $C_{17}H_{20}{}^{35}ClN_3O_2$

Intermediate 41: 4-*tert*-Butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carboxylic acid



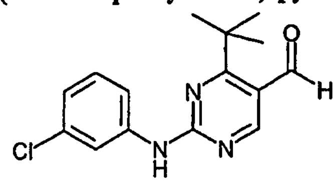
The title compound was prepared from 4-*tert*-butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carboxylic acid ethyl ester (3.79g) in a manner similar to the preparation of intermediate 20, but with a reflux time of 6.5 hours, to yield the title compound as an off white solid (3.02g).
NMR (d^6-DMSO) δ 1.42 (9H, s), 7.04 (1H, d), 7.32 (1H, t), 7.62 (1H, d), 8.10 (1H, s), 8.61 (1H, s).
LC/MS t= 4.10 min [MH^+]= 306 consistent with molecular formula $C_{15}H_{16}{}^{35}ClN_3O_2$

Intermediate 42: [4-*tert* -Butyl-2-(3-chloro-phenylamino)-pyrimidin-5-yl]-methanol



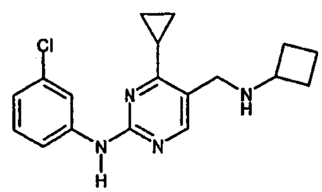
The title compound was prepared from 4-*tert*-butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carboxylic acid (2.09g) in a manner similar to intermediate 3, except that 5 minutes after the addition of the $NaBH_4$ (390 mg) in water (3mL), a further addition of sodium borohydride (390mg) in water (3mL) was made. After 5 minutes the reaction was quenched with water and worked up as before to yield the title compound as a pale yellow solid (1.63g).
NMR (d^6-DMSO) δ 1.40 (9H, s), 4.63 (2H, d), 5.18 (1H, t), 6.95 (1H, d), 7.28 (1H, t), 7.59 (1H, d), 8.12 (1H, s), 8.42 (1H, s), 9.74 (1H, s).
LC/MS t= 3.60 min [MH^+]= 292 consistent with molecular formula $C_{15}H_{18}{}^{35}ClN_3O$

Intermediate 43: 4-*tert*-Butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carbaldehyde



The title compound was prepared from [4-*tert*-butyl-2-(3-chloro-phenylamino)-pyrimidin-5-yl]-methanol (340mg) in a manner similar to intermediate 4 except that the reaction was heated for 5 hours, then stirred overnight, before being worked up in the same way to yield the title compound as a pale yellow solid (276mg).
NMR (d^6-DMSO) δ 1.46 (9H, s), 7.10 (1H, d), 7.36 (1H, t), 7.66 (1H, d), 8.17 (1H, s), 8.87 (1H, s), 10.33 (1H, s), 10.50 (1H brs).
LC/MS [MH^+]= 290 consistent with molecular formula $C_{15}H_{16}{}^{35}ClN_3O$

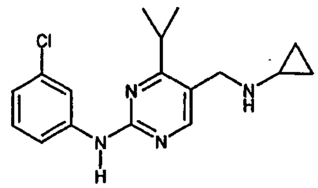
Example 1: (3-Chloro-phenyl)-(5-cyclobutylaminomethyl-4-cyclopropyl-pyrimidin-2-yl)-amine



2-(3-Chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carbaldehyde, (0.150g, 0.0548mmol, 1eq) in methanol (2ml) was added to 4A molecular sieves. Aminocyclobutane (0.156g, 0.219mmol, 4eq) was added, and the tube shaken for 1 hour. Glacial acetic acid (0.23g, 0.384mmol, 7eq) in dichloromethane (0.75ml) and MP-cyanoborohydride polymer reagent (Part number 800406, Argonaut Technologies Inc, 0.540g, 0.109mmol, 2eq) were added and the reaction mixture shaken for 48 hours. The polymer was filtered off, washed with methanol, and the filtrate evaporated in vacuo. The residue was purified by chromatography using the Biotage Horizon system described at the beginning of the experimental, to yield the title compound (0.034g, 0.0104mmol, 19%) as a white solid.
^{1}H NMR ($CDCl_3$) 1.37-1.50 (4H, m), 1.75-2.08 (2H, m), 2.32 (3H, brs), 2.56-2.69 (2H, m), 3.93 (1H, brs), 4.42 (2H, brs), 7.12 (1H, dd, J=8Hz, J=1Hz), 7.23 (1H, t, J=8Hz), 7.39 (1H, d, J=8Hz), 7.65 (1H, s), 9.41 (1H, s), 10.23 (1H, s), 11.05 (1H, s).

LC/MS t=2.49 min. Molecular ion observed [MH+] consistent with molecular formula $C_{18}H_{21}{}^{35}ClN_4$

Example 2: (3-Chloro-phenyl)-{5-[(cyclopropylmethyl-amino)-methyl]-4-isopropyl-pyrimidin-2-yl}-amine



The title compound prepared from 2-(3-chloro-phenylamino)-4-isopropyl-pyrimidine-5-carbaldehyde, and cyclopropylamine using the procedure described for Example 1 to yield the title compound.

NMR (DMSO-d6) δ -0.16- 0.02 (2H, m), 0.011-0.17 (2H, m), 1.00 (6H, d, J=7Hz), 1.80-1.87 (1H, m) 3.04-3.16 (1H, m), 3.46 (2H, s), 6.71 (1H, dd, J=8Hz, 2Hz), 7.04 (1H, t, J=8Hz), 7.43 (1H, dd, J=8Hz, J=1Hz), 7.95 (1H, t, J=2Hz), 8.08 (1H, s), 9.45 (1H, s).

LC/MS t=2.51 min. Molecular ion observed for [MH+] consistent with molecular formula $C_{17}H_{21}{}^{35}ClN_4$.

The compounds in Table 1 below were all prepared in a similar manner to the preparation of Example 1 by reductive amination of the appropriate aldehyde 2-(3-chloro-phenylamino)-4-cyclopropyl-pyrimidine-5-carbaldehyde or 2-(3-chloro-phenylamino)-4-isopropyl-pyrimidine-5-carbaldehyde with the appropriate amine. The amines used in the reductive aminations were all commercially available except for cyclopentylmethylamine hydrochloride which was prepared as described by Kelley et al in J Med Chem, 1997, 40, 3207, and used in place of the free base. The purification methods are given in the appropriate column of the Table:

Purification method A: Biotage 25S silica gel cartridge, using DCM/MeOH/AcOH/water - 120:15:3:2 as elutant

Purification method B: Trituration with MeOH

Purification method C: Biotage Horizon used, conditions given earlier.

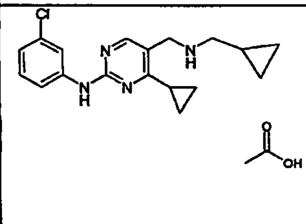
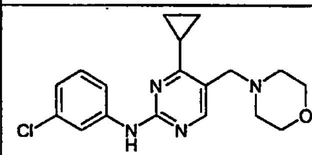
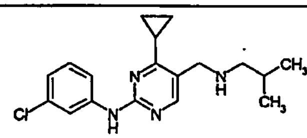
Purification method D: MDAP

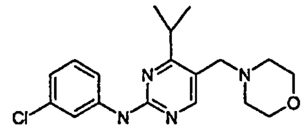
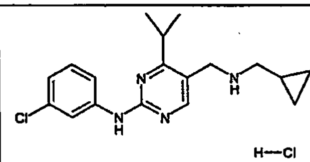
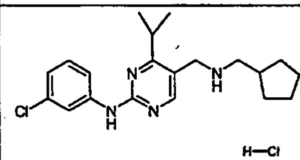
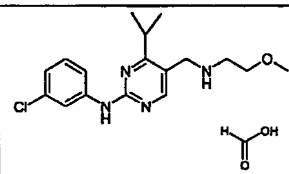
Purification method E: Biotage 25+M silica gel cartridge, using EtOAc:Isohexane 50:50 to 70:30, then trituration with MeOH

Purification method F: Biotage 25+M silica gel cartridge, EtOAc:isohexane 50:50. To product in Et_2O add cHCl, & evaporate

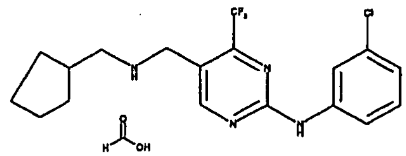
Purification method G: Biotage 25+M silica gel cartridge, EtOAc:isohexane 50:50 to 100%EtOAc. To product in Et_2O add cHCl, and evaporate

Table 1

Example	Name	Structure	Prep Method	Purification Method	LC/MS Retention Time, t (min) [M+] Molecular formula of free base NMR data
3	(3-Chloro-phenyl)-{4-cyclopropyl-5-[(cyclopropylmethyl-amino)-methyl]-pyrimidin-2-yl}-amine acetate		A	A	LC/MS t=2.46. NMR ($CDCl_3$) δ 0.26 (2H, d, J=5Hz),0.59 (2H, d, J=5Hz), 1.01-1.33 (5H, m), 2.11-2.20 (1H, m), 2.73 (2H, d, J=7Hz), 4.06 (2H, s) 6.97 (1H, d, J=7Hz), 7.19 (1H, t, J=8Hz), 7.33 (1H, d, J=8Hz), 7.87 (1H, s), 8.18 (1H, s), 8.67 (1H, brs), 9.80 (1H, brs).
4	(2-Chloro-phenyl)-(4-cyclopropyl-5-morpholin-4-ylmethyl-pyrimidin-2-yl)-amine		A	B	LC/MS t=2.57. NMR (DMSO) δ 1.03-1.12 (4H, m), 2.36-2.44 (4H, m), 2.64-2.68 (1H, m), 3.49 (2H, s) 3.53-3.59 (4H, m), 6.94 (1H, dd, J=8Hz, J=2Hz), 7.27 (1H, t, J=8Hz), 7.56 (1H, dd, J=8Hz, J=1Hz), 8.01 (1H, t, J=2Hz), 8.18 (1H, s), 9.64 (1H, s).
5	(3-Chloro-phenyl)-[4-cyclopropyl-5-(isobutylamino-methyl)-pyrimidin-2-yl]-amine		A	C	LC/MS t=2.42 [MH+] 331. Consistent with molecular formula $C_{18}H_{23}{}^{35}ClN_4$

6	(3-Chloro-phenyl)-(4-isopropyl-5-morpholin-4-ylmethyl-pyrimidin-2-yl)-amine		B	E	LC/MS t=2.79. NMR (DMSO-d6) δ 1.23 (6H, d, J=6Hz), 2.35 (4H, brs), 3.32-3.42 (1H, m), 3.54 (4H, t, J=4Hz), 6.94 (1H, dd, J=8Hz, J=1Hz), 7.19 (1H, t, J=8Hz), 7.33 (1H, d, J=8Hz), 7.28 (1H, t, J=8Hz), 7.64 (1H, dd, J=8Hz, J=1Hz), 8.14 (1H, t, J=2Hz), 8.25 (1H, s), 9.73 (1H,s).
7	(3-Chloro-phenyl)-{5-[(cyclopropylmethyl-amino)-methyl]-4-isopropyl-pyrimidin-2-yl}-amine hydrochloride		B	F	LC/MS t=2.56. NMR (DMSO-d6) δ 0.39-0.45 (2H, m), 0.56-0.63 (2H, m), 1.14-1.30 (7H, m), 2.87-2.96 (2H, m), 3.32-3.43 (1H, m) 4.13 (2H, t, J=8Hz), 6.43 (>2H, brs), 7.00 (1H, dd, J=8Hz, J=2Hz), 7.32 (1H, t, J=8Hz), 7.66 (1H, dd, J=8Hz, J=1Hz), 8.15 (1H, t, J=1Hz), 8.67 (1H, s), 9.64 (1H, brs), 10.00, (1H, s).
8	(3-Chloro-phenyl)-{5-[(cyclopentylmethyl-amino)-methyl]-4-isopropyl-pyrimidin-2-yl}-amine hydrochloride		B	G	LC/MS t=2.91. NMR (DMSO-d6) δ 0.89-1.30 (10H, m), 1.57-1.87 (5H, m), 2.85 (2H, brs), 3.36 (1H, t, J=8Hz), 4.12 (2H, brs), 5.37 (>2H, brs), 6.99 (1H, d, J=8Hz), 7.32 (1H, t, J=8Hz), 7.65 (1H, d, J=8Hz), 8.14 (1H, s), 8.63 (1H, s), 9.02 (1H, brs), 9.93 (1H, s).
9	(3-Chloro-phenyl)-{4-isopropyl-5-[(2-methoxy-ethylamino)-methyl]-pyrimidin-2-yl}-amine formate		A	D	LC/MS t=2.44 [MH+] 335. Consistent with molecular formula $C_{17}H_{23}{}^{35}ClN_4O$

Example 10: (3-Chlorophenyl)-{5-[(cyclopentylmethylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine, formate

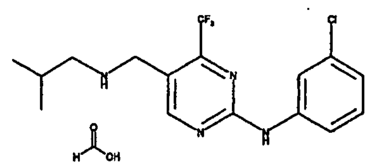


To a solution of 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde, (120 mg) in methanol (2 ml) was added powdered 4A molecular sieves (100 mg) followed by cyclopentylmethylamine hydrochloride (106 mg prepared as described in Kelley et al., J. Med. Chem., 40, 3207, (1997)) in methanol (2 ml). The mixture was shaken in a capped Alltech extract-clean filter column (8 ml) for 2h. Glacial acetic acid (136 uL) was added followed by MP-Cyanoborohydride (Argonaut Technologies) (390 mg) and the mixture shaken for 6h. The mixture was filtered and the MP-Cyanoborohydride washed with methanol (2 x 4 ml). The filtrate was applied to a methanol conditioned SCX column (2 g) and eluted with methanol. The column was then eluted with 2% 880 ammonia in methanol and the solution collected and evaporated under reduced pressure. Purified by Mass-directed autopurification using the procedures detailed at the beginning of the experimental to afford (3-chlorophenyl)-{5[(cyclopentylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2yl}-amine, formate (64 mg).

NMR (MeOD) δ 1.28 (2H, m), 1.69 (4H, m), 1.90 (2H, m), 2.19 (1H, m), 2.99 (2H, d), 4.20 (2H, s), 7.04 (1H, dd), 7.29 (1H, t), 7.57 (1H, dd), 7.97 (1H, s), 8.43 (1H, s), 8.80 (1H, s).

LC/MS, t = 2.76 min, molecular ion observed [MH^+] 385, consistent with $C_{18}H_{20}ClF_3N_4$

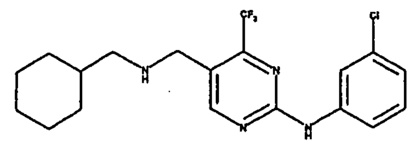
Example 11: (3-Chlorophenyl)-{5-[(isobutylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine, formate



To a solution of 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde, (60 mg) in methanol (1 ml) was added powdered 4A molecular sieves (30 mg) followed by isobutylamine (15 mg) in methanol (1 ml). The mixture was shaken in a capped Alltech extract-clean filter column (8 ml) for 1h. Polymer-supported borohydride on Amberlite (Aldrich) (95 mg) was added and the mixture shaken overnight. The mixture was filtered and the polymer-supported borohydride washed with methanol (2 x 4 ml). The combined filtrate was applied to a methanol conditioned SCX column (2 g) and eluted with methanol. The column was then eluted with 2% aqueous 0.880 ammonia in methanol and the eluant evaporated under reduced pressure. The residue was purified by MDAP using the procedures detailed at the beginning of the experimental to afford (3-chlorophenyl)-{5-[(isobutylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine, formate (30 mg).

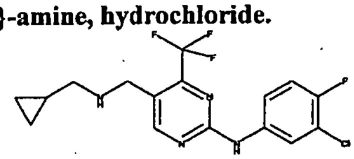
NMR (MeOD) δ 1.00 (6H, d), 2.00 (1H, m), 1.90 (2H, m), 2.85 (2H, d), 4.20 (2H, s), 7.04 (1H, dd), 7.29 (1H, t), 7.57 (1H, dd), 7.97 (1H, s), 8.43 (1H, s), 8.80 (1H, s).
LC/MS, t = 2.78 min, molecular ion observed [M-H$^+$] 357.

Example 12: (3-Chlorophenyl)-{5-[(cyclohexylmethylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine



To a solution of (5-bromomethyl-4-trifluoromethyl-pyrimidin-2-yl)-(3-chloro-phenyl)-amine, (25 mg) in tetrahydrofuran (1 ml) was added a solution of cyclohexanemethylamine (200 mg) in tetrahydrofuran (1 ml) and the solution stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The residue was co-evaporated from dichloromethane and a few drops of triethylamine. The residue was purified by chromatography on a Waters Se-pak cartridge of silica gel, eluting with ether : dichloromethane 1 : 10 to afford the title compound as a white solid (24 mg).
NMR (DMSO-d6) δ 0.85 (2H, q), 1.14-1.23 (>3H, m), 1.4 (1H, m), 1.63-1.75 (5H, m), 2.34 (2H, d), 3.73 (2H, s), 7.03 (1H, dd), 7.33 (1H, t), 7.66 (1H, dd), 7.99 (1H, s), 8.86 (1H, s), 10.30 (1H, s)
LC/MS, t = 2.92 min, molecular ion observed [MH$^+$] 399, consistent with $C_{19}H_{22}{}^{35}ClF_3N_4$

Example 13: A (3-Chloro-4-fluoro-phenyl)-{5-[(cyclopropylmethyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, hydrochloride.



To [2-(3-chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-cyclopropylmethyl-carbamic acid dimethyl-ethyl ester, (58 mg) was added 4N hydrogen chloride in dioxan (2 ml) and the solution stirred at room temperature for 1h. The solution was evaporated under reduced pressure to afford the title compound as a yellow foam (50 mg).
NMR (DMSO-d6) δ 0.39 (2H, m), 0.59 (2H, m), 1.12 (1H, m), 2.91 (2H, d), 4.22 (2H, s), 7.42 (1H, t), 7.68 (1H, m), 8.06 (1H, m), 9.06 (1H, s), 9.39 (2H, s), 10.40 (1H, s).
LC/MS, t = 2.65 min, molecular ion observed [M+H$^+$] 375, consistent with $C_{16}H_{15}ClF_4N_4$.

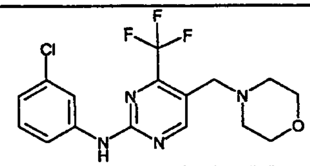
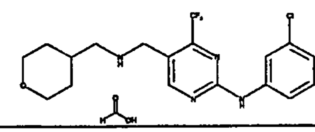
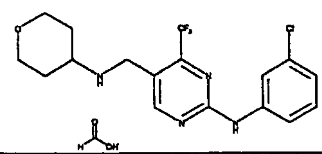
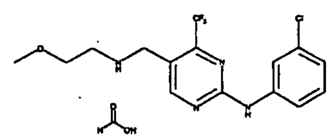
The Examples in the Table 2 were prepared in a similar manner to the methods described above:

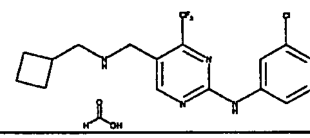
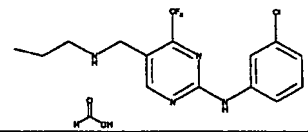
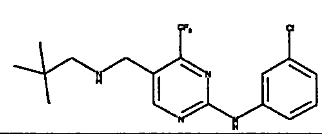
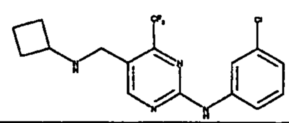
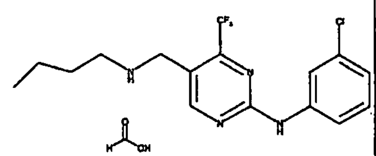
Prep Method D: Reductive amination as described for Example 96 using four equivalents of the appropriate amine.
Prep Method E: Reductive amination as described for method D using the appropriate known amine and aldehyde, the syntheses of which are described above.
Prep Method F: Reductive amination as described for method E using two to four equivalents of the appropriate amine and tetrahdrofuran as the solvent.

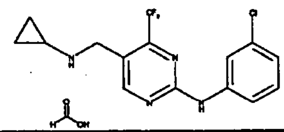
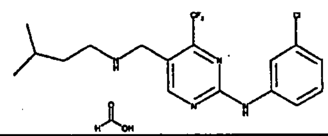
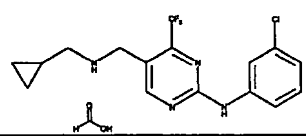
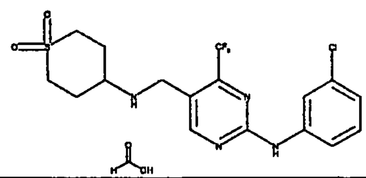
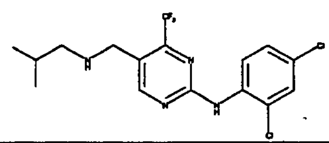
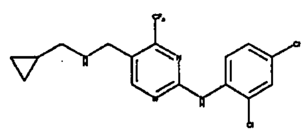
Prep Method G: Treatment of the corresponding BOC compound with 4N hydrogen chloride in 1,4-dioxan.
Prep Method H: As described for Example 12
Purification method A: Purify using an SCX column followed by the MDAP system detailed at the beginning of the experimental section as described for Example 10
Purification method B: Purify using the MDAP system detailed at the beginning of the experimental section.
Purification method C: Purify using an SCX column followed by the Biotage Horizon system detailed at the beginning of the experimental section.
Purification method D: Purify using the Biotage Horizon system detailed at the beginning of the experimental section.
Purification method E: Purify by trituration with methanol.
Purification method F: Purify by trituration with diethyl ether.
Purification method G: Purify as described for Example 12.

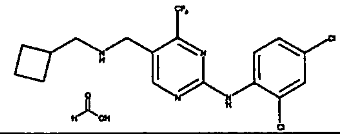
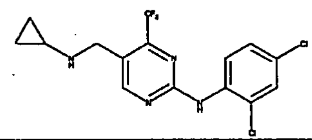
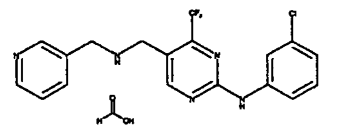
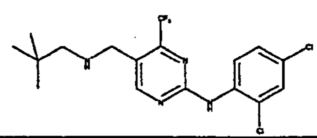
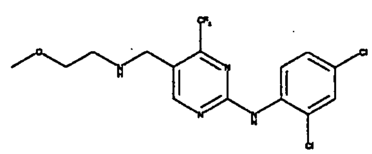
Example 26 was prepared using tetrahydro-2*H*-thiopyran-4-amine 1,1-dioxide hydrochloride which may be prepared as described by N Sakai in Patent No WO 2003072554.

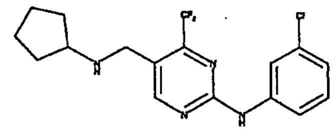
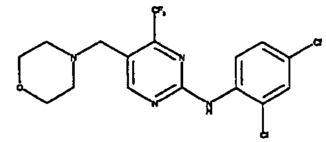
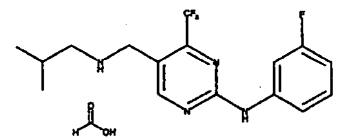
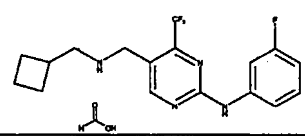
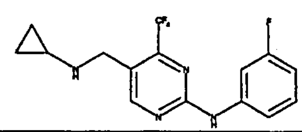
Table 2

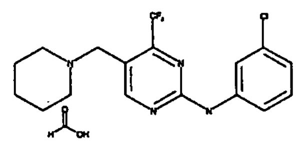
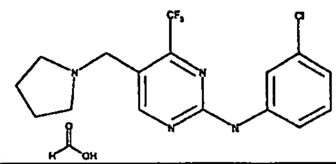
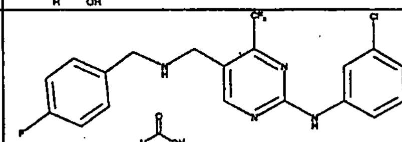
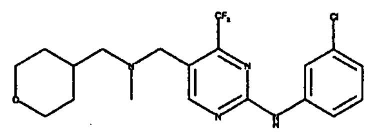
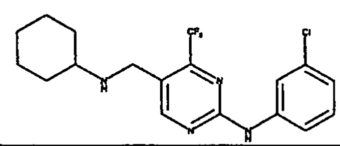
Example	Name	Structure	Prep Method	Purification Method	Ret Time (min) [M+] Molecular formula of free base
14	(3-Chlorophenyl)-(5-morpholin-4-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		F	A	3.19 373 $C_{16}H_{16}{}^{35}Cl\,F_3N_4O$
15	(3-Chlorophenyl)-(5-{[(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		D	A	2.52 401 $C_{18}H_{20}{}^{35}Cl\,F_3N_4O$
16	(3-Chlorophenyl)-{5-[(tetrahydro-pyran-4-ylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		D	A	2.49 387 $C_{17}H_{18}{}^{35}Cl\,F_3N_4O$
17	(3-Chlorophenyl)-{5- [(2-methoxy-ethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		D	A	2.51 361 $C_{15}H_{16}{}^{35}Cl\,F_3N_4O$

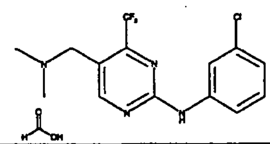
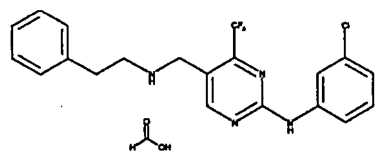
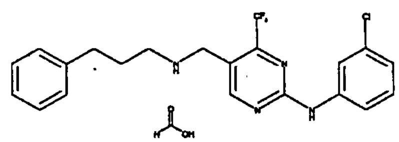
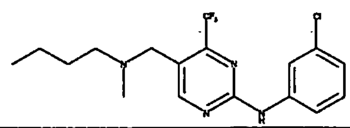
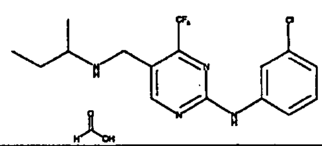
18	(3-Chlorophenyl)-{5-[(cyclobutylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		D	A	2.70 371 $C_{17}H_{18}{}^{35}Cl\ F_3N_4$
19	(3-Chlorophenyl)-(5-propylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		D	A	2.56 345 $C_{15}H_{16}{}^{35}Cl\ F_3N_4$
20	(3-Chlorophenyl)-{5- [(2,2-dimethylpropylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		D	D	2.74 373 $C_{17}H_{20}{}^{35}Cl\ F_3N_4$
21	(3-Chlorophenyl)-(5-cyclobutylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		D	D	2.59 357 $C_{16}H_{16}{}^{35}Cl\ F_3N_4$
22	(3-Chlorophenyl)-(5-butylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		D	A	2.67 359 $C_{16}H_{18}{}^{35}Cl\ F_3N_4$

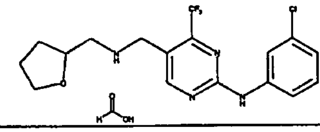
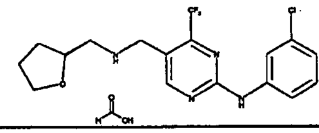
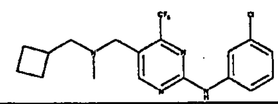
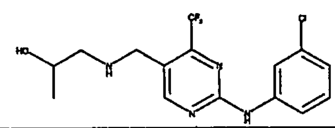
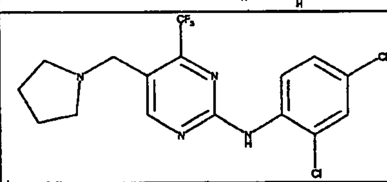
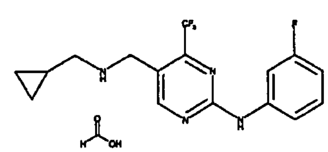
23	(3-Chlorophenyl)-(5-cyclopropylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		D	A	2.61 343 $C_{15}H_{14}{}^{35}Cl\ F_3N_4$
24	(3-Chlorophenyl)-{5- [(3-methylbutylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		D	A	2.78 373 $C_{17}H_{20}{}^{35}Cl\ F_3N_4$
25	(3-Chlorophenyl)-{5-[(cyclopropylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		D	A	2.60 357 $C_{16}H_{16}{}^{35}Cl\ F_3N_4$
26	(3-Chlorophenyl)-{5- [(1,1-dioxo-hexahydro-1l^6-thiopyran-4-ylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		D	B	2.74 435 $C_{17}H_{18}{}^{35}Cl\ F_3N_4O_2S$
27	(2,4-Dichlorophenyl)-{5-[(isobutylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine.		E	C	2.71 393 $C_{16}H_{17}{}^{35}Cl_2F_3N_4$
28	(2,4-Dichlorophenyl)-{5-[(cyclopropylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		E	C	2.67 391 $C_{16}H_{15}{}^{35}Cl_2F_3N_4$

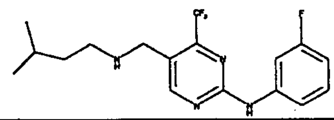
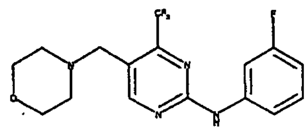
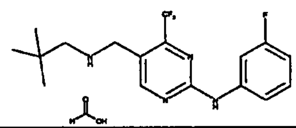
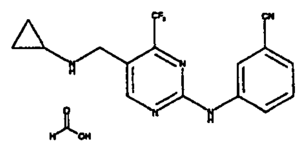
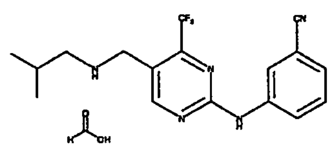
29	(2,4-Dichlorophenyl)-{5-[(cyclobutylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		E	A	2.80 405 $C_{17}H_{17}{}^{35}Cl_2F_3N_4$
30	(2,4-Dichlorophenyl)-(5-cyclopropylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		E	A	2.74 377 $C_{15}H_{13}{}^{35}Cl_2F_3N_4$
31	(3-Chlorophenyl)-(5-{[(pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		D	B	2.65 394 $C_{18}H_{15}{}^{35}Cl\,F_3N_5$
32	(2,4-Dichlorophenyl)-{5- [(2,2-dimethylpropylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		E	B	2.86 407 $C_{17}H_{19}{}^{35}Cl_2F_3N_4$
33	(2,4-Dichlorophenyl)-{5- [(2-methoxy-ethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		E	B	2.60 395 $C_{15}H_{15}{}^{35}Cl_2F_3N_4O$

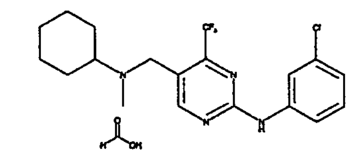
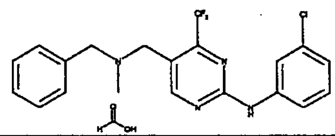
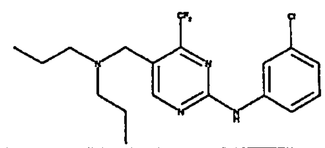
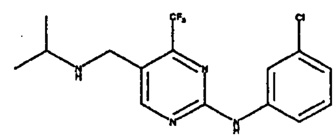
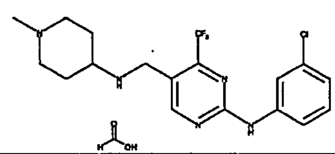
34	(3-Chlorophenyl)-(5-cyclopentylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		D	D	2.66 371 $C_{17}H_{18}{}^{35}Cl\,F_3N_4$
35	(2,4-Dichlorophenyl)-(5-morpholin-4-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		F	E	3.54 407 $C_{16}H_{15}{}^{35}Cl_2F_3N_4O$
36	(3-Fluorophenyl)-{5-[(isobutylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine, formate		E	B	2.55 343 $C_{16}H_{18}F_4N_4$
37	(3-Fluorophenyl)-{5-[(cyclobutylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		E	B	2.63 355 $C_{17}H_{18}F_4N_4$
38	(3-Fluorophenyl)-(5-cyclopropylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		E	B	2.46 327 $C_{15}H_{14}F_4N_4$

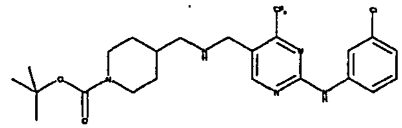
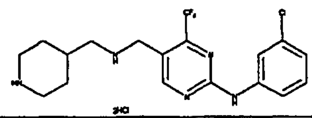
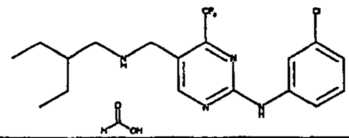
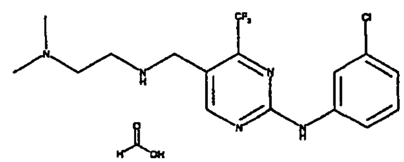
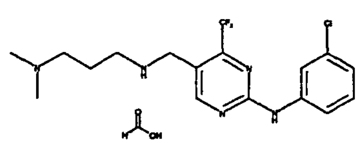
39	(3-Chlorophenyl)-(5-piperidin-1-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		F	A	2.60 371 $C_{17}H_{18}{}^{35}Cl\ F_3N_4$
40	(3-Chlorophenyl)-(5-pyrrolidin-1-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate.		F	A	2.52 357 $C_{16}H_{16}{}^{35}Cl\ F_3N_4$
41	(3-Chlorophenyl)-{5-[(4-fluorobenzylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		D	A	2.89 411 $C_{19}H_{15}{}^{35}Cl\ F_4N_4$
42	(3-Chlorophenyl)-(5-{[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine		F	A	2.60 415 $C_{19}H_{22}{}^{35}Cl$ F_3N_4O
43	(3-Chlorophenyl)-(5-cyclohexylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		D	C	2.72 385 $C_{18}H_{20}{}^{35}Cl\ F_3N_4$

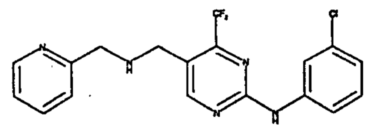
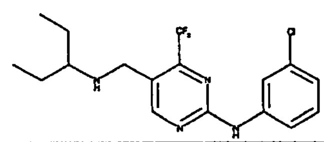
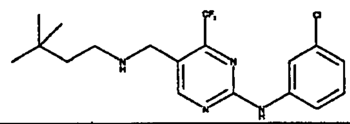
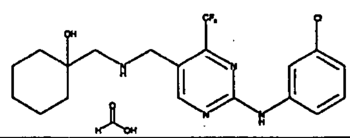
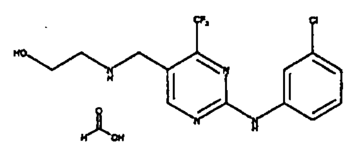
44	(3-Chlorophenyl)-(5-dimethylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate.		D	A	2.46 331 $C_{14}H_{14}{}^{35}Cl\ F_3N_4$
45	(3-Chlorophenyl)-[5-(phenethylamino-methyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine, formate.		D	B	2.83 407 $C_{20}H_{18}{}^{35}Cl\ F_3N_4$
46	(3-Chlorophenyl)-[5-(phenpropylamino-methyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine, formate.		D	B	2.92 421 $C_{21}H_{20}{}^{35}Cl\ F_3N_4$
47	{5-[(Butyl-methyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-(3-chlorophenyl)-amine		D	A	2.73 373 $C_{17}H_{20}{}^{35}Cl\ F_3N_4$
48	[5-(sec-Butylamino-methyl)-4-trifluoromethyl-pyrimidin-2-yl]-(3-chloro-phenyl)-amine, formate.		D	A	2.63 359 $C_{16}H_{18}{}^{35}Cl\ F_3N_4$

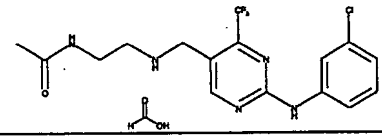
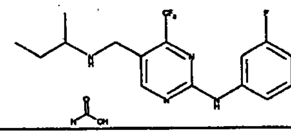
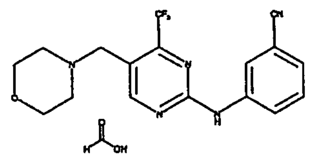
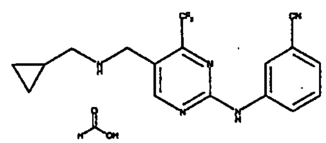
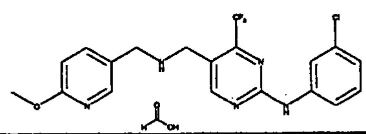
49	(3-Chlorophenyl)-(5-{[[(2R)-tetrahydro-furan-2-ylmethyl]-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate.		D	A	2.62 387 $C_{17}H_{18}{}^{35}Cl\ F_3N_4O$
50	(3-Chlorophenyl)-(5-{[[(2S)-tetrahydro-furan-2-ylmethyl]-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate.		D	A	2.61 387 $C_{17}H_{18}{}^{35}Cl\ F_3N_4O$
51	(3-Chlorophenyl)-{5-[(cyclobutylmethyl-methyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine		F	D	2.78 385 $C_{18}H_{20}{}^{35}Cl\ F_3N_4$
52	1-{[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-amino}-propan-2-ol		D	D	2.46 361 $C_{15}H_{16}{}^{35}Cl\ F_3N_4O$
53	(2,4-Dichlorophenyl)-(5-pyrrolidin-1-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		F	D	2.69 405 $C_{17}H_{17}{}^{35}Cl_2F_3N_4$
54	(3-Fluorophenyl)-{5-[(cyclopropylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		E	B	2.51 341 $C_{16}H_{16}F_4N_4$

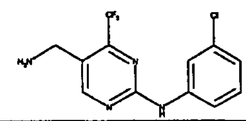
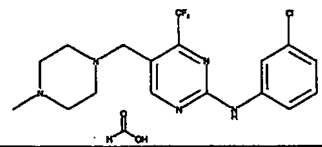
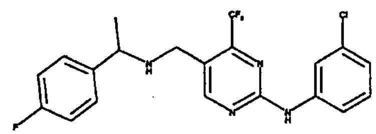
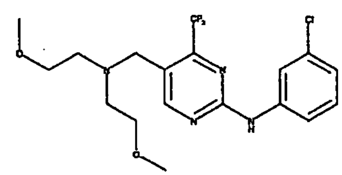
55	(3-Fluorophenyl)-{5- [(3-methylbutylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		E	D	2.69 357 $C_{17}H_{20}F_4N_4$
56	(3-Fluorophenyl)-(5-morpholin-4-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		F	B	2.98 357 $C_{16}H_{16}F_4N_4O$
57	(3-Chlorophenyl)-{5- [(2,2-dimethylpropylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		E	B	2.67 357 $C_{17}H_{20}F_4N_4$
58	(3-Cyanophenyl)-(5-cyclopropylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		E	B	2.36 334 $C_{16}H_{14}F_3N_5$
59	(3-Cyanophenyl)-{5-[(isobutylamino)-methyl]-4- trifluoromethyl-pyrimidin-2yl}-amine, formate		E	B	2.45 350 $C_{17}H_{18}F_3N_5$

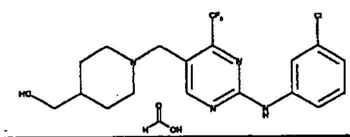
60	(3-Chlorophenyl)-{5-[(cyclohexylmethyl-methyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		F	A	2.78 399 $C_{19}H_{22}{}^{35}Cl\ F_3N_4$
61	(3-Chlorophenyl)-{5-[(benzylmethyl-methyl-amino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		F	A	3.20 407 $C_{20}H_{18}{}^{35}Cl\ F_3N_4$
62	(3-Chlorophenyl)-(5-dipropylaminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine.		D	B	2.92 387 $C_{18}H_{22}{}^{35}Cl\ F_3N_4$
63	(3-Chlorophenyl)-[5-(isopropylamino-methyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine.		D	D	2.55 345 $C_{15}H_{16}{}^{35}Cl\ F_3N_4$
64	(3-Chloro-phenyl)-{5-[(1-methyl-piperidin-4-ylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		D	B	2.26 400 $C_{18}H_{21}{}^{35}Cl\ F_3N_5$

65	4-({[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-amino}-methyl)-piperidine-1-carboxylic acid tert -butyl ester.		D	D	2.93 500 $C_{23}H_{29}{}^{35}Cl\ F_3N_5O_2$
66	(3-Chlorophenyl)-(5-{[(piperidin-4-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine, dihydrochloride.		G	F	2.20 400 $C_{18}H_{21}{}^{35}Cl\ F_3N_5$
67	(3-Chlorophenyl)-{5-[(2-ethyl-butylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		D	B	2.90 387 $C_{18}H_{22}{}^{35}Cl\ F_3N_4$
68	N-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]- N', N'-dimethyl-ethane-1,2-diamine, formate		D	B	2.57 374 $C_{16}H_{19}{}^{35}Cl\ F_3N_5$
69	N-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]- N', N'-dimethyl-propane-1,2-diamine, formate.		D	A	2.12 388 $C_{17}H_{21}{}^{35}Cl\ F_3N_5$

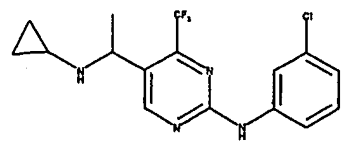
70	(3-Chlorophenyl)-(5-{[(pyridin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine.		D	B	2.69 394 $C_{18}H_{15}{}^{35}Cl\ F_3N_5$
71	(3-Chlorophenyl)-{5-[(1-ethyl-propylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		D	D	2.72 373 $C_{17}H_{20}{}^{35}Cl\ F_3N_4$
72	(3-Chlorophenyl)-{5-[(3,3-dimethyl-butylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		D	D	2.85 387 $C_{18}H_{22}{}^{35}Cl\ F_3N_4$
73	1-({[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-amino}-methyl)-cyclohexanol, formate		D	B	2.70 415 $C_{19}H_{22}{}^{35}Cl\ F_3N_4O$
74	2-{[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-amino}-ethanol, formate.		D	B	2.42 347 $C_{14}H_{14}{}^{35}Cl\ F_3N_4O$

75	N-(2-{[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-amino}-ethyl)-acetamide, formate		D	B	2.44 388 $C_{16}H_{17}{}^{35}Cl\ F_3N_5O$
76	[5-(sec-Butylamino-methyl)-4-trifluoromethyl-pyrimidin-2-yl]-(3-fluoro-phenyl)-amine, formate.		E	B	2.53 343 $C_{16}H_{18}F_4N_4$
77	(3-Cyanophenyl)-(5-morpholin-4-ylmethyl-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate.		E	A	2.85 364 $C_{17}H_{16}F_3N_5O$
78	(3-Cyanophenyl)-{5-[(cyclopropylmethylamino)-methyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		E	B	2.39 348 $C_{17}H_{16}F_3N_5$
79	(3-Chloro-phenyl)-(5-{[(6-methoxy-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate.		D	B	2.72 424 $C_{19}H_{17}{}^{35}Cl\ F_3N_5O$

80	(5-Aminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-(3-chlorophenyl)-amine.		H	G	2.47 303 $C_{12}H_{10}{}^{35}Cl\ F_3N_4$
81	(3-Chlorophenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine, formate.		F	A	2.61 386 $C_{17}H_{19}{}^{35}Cl\ F_3N_5$
82	(3-Chlorophenyl)-(5-{[1-(4-fluoro-phenyl)-ethylamino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine		D	D	3.00 425 $C_{20}H_{17}{}^{35}Cl\ F_4N_4$
83	(5-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2-yl)-(3-chlorophenyl)-amine.		D	D	3.26 419 $C_{18}H_{22}{}^{35}Cl\ F_3N_4O_2$

84	{1-[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-ylmethyl]-piperidin-4-yl}-methanol, formate.		F	B	2.48 401 $C_{18}H_{20}{}^{35}Cl$ F_3N_4O

Example 85 : 3-Chlorophenyl)-[5-(1-cyclopropylamino-ethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine

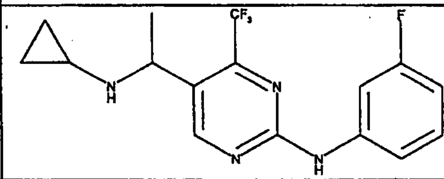
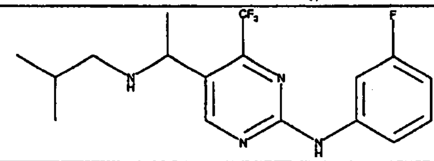
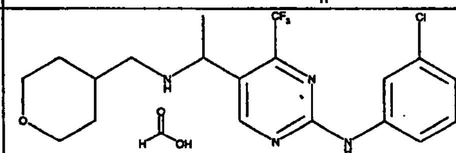
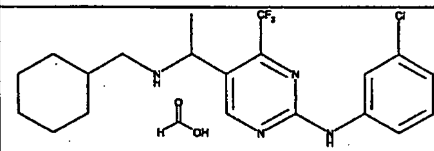


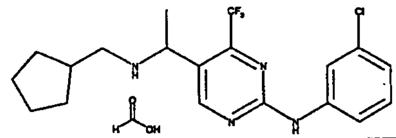
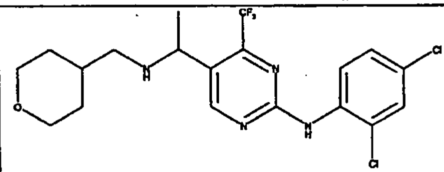
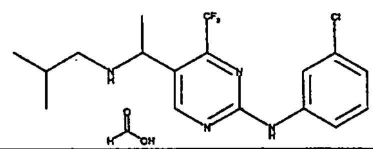
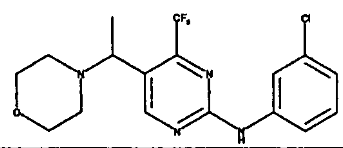
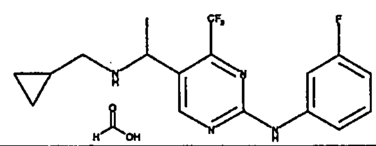
To a solution of 1-[2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-ethanone (80 mg) in methanol (1.0 ml) was added powdered 4A molecular sieves (70 mg) followed by cyclopropylamine (57 mg) in methanol (1.0 ml). The mixture was shaken in a capped Alltech extract-clean filter column (8 ml) for 0.5h. Glacial acetic acid (106 mg) in dichloromethane (1 ml) was added followed by MP-Cyanoborohydride (Argonaut Technologies) (248 mg) and the mixture shaken for 84h. MP-Cyanoborohydride (248 mg) was added and the mixture shaken for 20h. The mixture was filtered and the MP-Cyanoborohydride washed with methanol (2 x 4 ml). The combined filtrates were evaporated under reduced pressure and the residue purified by Mass-directed autopurification using the procedures detailed at the beginning of the experimental to afford (3-chlorophenyl)-[5-(1-cyclopropylamino-ethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine (29 mg).
NMR (MeOD) δ 0.21-0.45 (4H, m), 1.40 (3H, d), 1.95 (1H, m), 4.23 (1H, m), 6.95 (1H,d), 7.25 (1H, t), 7.58 (1H, d), 8.00 (1H, s), 9.50 (1H, s).
LC/MS, t = 2.75 min, molecular ion observed [M-H$^+$] 355, consistent with $C_{16}H_{16}ClF_3N_4$.

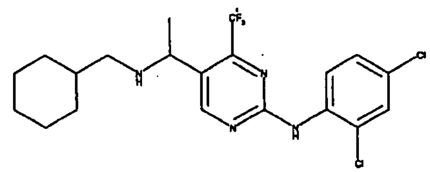
The Examples in Table 3 were prepared as follows.
Prep Method A: Reductive amination as described for Example 85
Prep Method B: Reductive amination as described for Example 85 using an excess of zinc chloride in tetrahydrofuran, and shaking overnight, prior to the addition of acetic acid and MP-cyanoborohydride.
Prep Method C: Reductive amination as described for Example 85 using titanium isopropoxide (2 eq) and microwave heating at 160°C for 3 x 10 minutes to form the imine prior to the addition of the acetic acid and MP-Cyanoborohydride. Reaction times between 3 and 14 days.
Prep Method D: Reductive amination as described for Example 85 using zinc chloride and microwave heating at 180°C for 15 minutes to form the imine prior to the addition of the acetic acid and MP-Cyanoborohydride.
Prep Method E: Reductive amination as described for Example 85 using tetrahydrofuran as solvent.

Purification method A: Purify using an SCX column followed by the MDAP system detailed at the beginning of the experimental section as described for Example 10 .
Purification method B: Purify using the MDAP system detailed at the beginning of the experimental section.

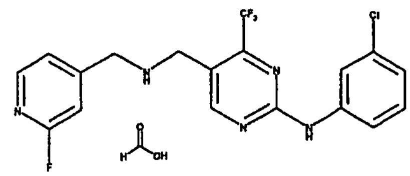
Table 3

Example	Name	Structure	Preparation Method	Purification Method	Ret Time (min) [M+] Molecular Formula of free base
86	(3-Fluorophenyl)-[5-(1-cyclopropylamino-ethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine		B	B	2.58 341 $C_{16}H_{16}F_4N_4$
87	(3-Fluorophenyl)-[5-(1-isobutylamino-ethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine		B	B	2.62 357 $C_{17}H_{20}F_4N_4$
88	(3-Chlorophenyl)-(5-{1-[(tetrahydro-pyran-4-ylmethyl)-amino]-ethyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine, formate		C	B	2.53 415 $C_{19}H_{22}{}^{35}Cl\,F_3N_4O$
89	(3-Chlorophenyl)-{5-[1-(cyclohexylmethyl-amino)-ethyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		C	A	2.92 413 $C_{20}H_{24}{}^{35}Cl\,F_3N_4$

90	(3-Chlorophenyl)-{5-[1-(cyclopentylmethyl-amino)-ethyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate.		C	A	2.80 399 $C_{19}H_{22}{}^{35}Cl\ F_3N_4$
91	(2,4-Dichlorophenyl)-(5-{1-[(tetrahydro-pyran-4-ylmethyl)-amino]-ethyl}-4-trifluoromethyl-pyrimidin-2-yl)-amine.		C	B	2.53 449 $C_{19}H_{21}{}^{35}Cl_2$ F_3N_4O
92	(3-Chlorophenyl)-[5-(1-isobutylamino-ethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine, formate		D	B	2.76 373 $C_{17}H_{20}{}^{35}Cl\ F_3N_4$
93	(3-Chlorophenyl)-[5-(1-morpholin-4-yl-ethyl)-4-trifluoromethyl-pyrimidin-2-yl]-amine		E	B	3.57 387 $C_{17}H_{18}{}^{35}Cl$ F_3N_4O
94	(3-Fluorophenyl)-{5-[1-(cyclopropylmethyl-amino)-ethyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine, formate		A	B	2.58 355 $C_{17}\ H_{28}F_4N_4$

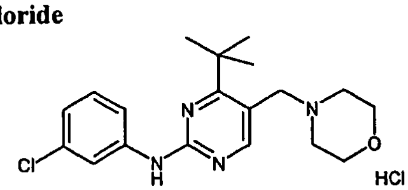
95	(2,4-Dichlorophenyl)-{5-[1-(cyclohexylmethyl-amino)-ethyl]-4-trifluoromethyl-pyrimidin-2-yl}-amine.		C	B	3.00 447 $C_{20}H_{23}{}^{35}Cl_2F_3N_4$

Example 96: (3-Chlorophenyl)-(5-{[(2-fluoropyridin-4-ylmethyl)-amino]-methyl}-4-trifluoromethyl-pyrimidin-2yl}-amine, formate



To a solution of 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carbaldehyde (100 mg) in methanol (1.5 ml) was added powdered 4A molecular sieves (70 mg) followed by C-(2-fluoro-pyridin-4-yl)-methylamine dihydrochloride (Intermediate 36) (81 mg) in methanol (1.5 ml). The mixture was shaken in a capped Alltech extract-clean filter column (8 ml) for 0.5h. Glacial acetic acid (139 mg) in dichloromethane (1 ml) was added followed by MP-Cyanoborohydride (Argonaut Technologies) (330 mg) and the mixture shaken overnight. The mixture was filtered and the MP-Cyanoborohydride washed with methanol (2 x 4 ml). The filtrate was applied to a methanol conditioned SCX column (2 g) and eluted with methanol. The column was then eluted with 2% aqueous 0.880 ammonia in methanol and the filtrate evaporated under reduced pressure. The residue was purified by MDAP using the procedures detailed at the beginning of the experimental to afford (3-chlorophenyl)-(5-{[(2-fluoropyridin-4-ylmethyl)-amino]-methyl}-4- trifluoromethyl-pyrimidin-2yl}-amine, formate (50 mg)
NMR (MeOD) δ 3.88 (2H, s), 3.95 (2H, s), 6.99 (1H, d), 7.13 (1H, s), 7.26 (1H, t), 7.33 (1H, d), 7.55 (1H, d), 7.96 (1H, s), 8.13 (2H, d), 8.79 (1H, s).
LC/MS, t = 3.17 min, molecular ion observed [MH^+] 412.

Example 97: (4-*tert*-Butyl-5-morpholin-4-ylmethyl-pyrimidin-2-yl)-(3-chloro-phenyl)-amine hydrochloride



A mixture of (4-*tert*-butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carbaldehyde (100mg), morpholine (0.120ml), and glacial acetic acid (0.0198ml) in THF (2ml) was stirred with 4A molecular sieves (65mg) at 21°C for 2 hours. Sodium triacetoxyborohydride (103mg) and THF (2ml) was added and stirring continued for 16 hours. The reaction mixture was filtered through a bed of Kieselguhr and this washed with EtOAc (10ml). The solution was then washed with aqueous 1M NaOH and backwashed with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$), and the volatiles were removed in vacuo to yield the crude product. The crude product was purified using MDAP. Excess ethereal HCl was added to the product and the

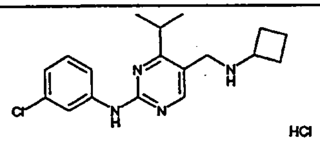
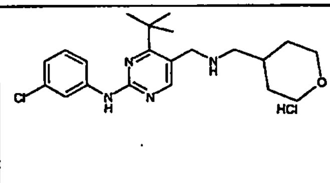
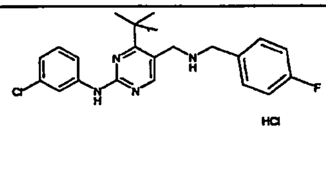
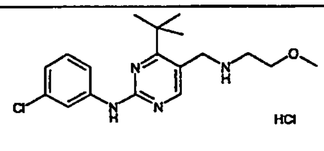
resultant precipitate was filtered off, dried at 50°C under vaccum to yield the title compound as a white solid (12mg).

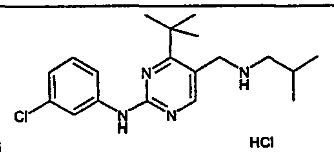
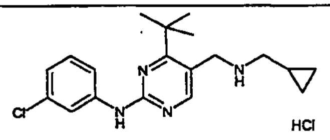
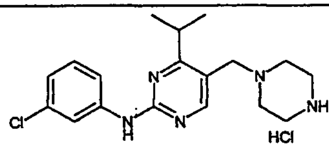
NMR (d^6-DMSO) δ 2.50 (9H, s), 3.25-3.43 (4H, m), 3.80-3.98 (4H, m), 4.58 (2H, brs), 7.00 (1H, d), 7.31 (1H, t), 7.60 (1H, m), 8.14 (1H, s), 8.88 (1H, s), 10.00 (1H, s), 10.20 (1H, s).

LC/MS t= 3.93 min [MH^+]= 361 consistent with molecular formula $C_{19}H_{25}{}^{35}ClN_4O.HCl$

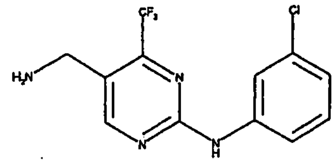
The products in Table 4 were prepared in a similar method to the preparation of Example 97 from 2-(3-chloro-phenylamino)-4-isopropyl-pyrimidine-5-carbaldehyde or 4-*tert*-butyl-2-(3-chloro-phenylamino)-pyrimidine-5-carbaldehyde as appropriate.

Table 4

Example No	Structure	Name	LC/MS Retention Time, t (min) [MH$^+$] Molecular formula of free base NMR data
98		(3-Chloro-phenyl)-{5-[(cyclobutylamino)-methyl]-4-isopropyl-pyrimidin-2-yl}-amine hydrochloride	NMR (d^6-DMSO) δ 1.23 (6H, d), 1.48-1.74 (4H, m), 2.04-2.15 (2H, m), 3.11-3.20 (1H, m), 3.28-3.40 (2H, m), 3.53 (H, s), 6.93 (1H, d), 7.28 (1H, t), 7.64 (1H, d), 8.17 (1H, s), 8.29 (1H, s), 9.69 (1H, s).
99		(4-*tert* -Butyl-5-{[(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-pyrimidin-2-yl)-(3-chloro-phenyl)-amine hydrochloride	LC/MS t=2.76. [MH$^+$]= 389 $C_{21}H_{29}{}^{35}ClN_4O$ NMR (MeOD) δ 1.33-1.46 (4H, m), 1.48 (9H, s), 1.76 (2H, d), 2.00-2.10 (1H, m), 3.40-3.50 (2H, m), 3.98 (2H, dd), 4.46 (2H, s), 7.00 (1H, d), 7.26 (1H, t), 7.48 (1H, d), 8.06 (1H, t), 8.49 (1H, s).
100		(4-*tert* -Butyl-5-[(4-fluoro-benzylamino)-methyl]-pyrimidin-2-yl}-(3-chloro-phenyl)-amine hydrochloride	LC/MS t=3.16. [MH$^+$]= 399 $C_{22}H_{24}{}^{35}ClFN_4$ NMR (MeOD) δ 1.36 (9H, s), 4.40 (2H, s) 4.43 (2H, s), 6.99 (1H, d), 7.22-7.28 (3H, m), 7.46 (1H, d), 7.58-7.62 (2H, m), 8.04 (1H, t), 8.44 (1H, s).
101		(4-*tert* -Butyl-5-[(2-methoxy-ethylamino)-methyl]-pyrimidin-2-yl}-(3-chloro-phenyl)-amine hydrochloride	LC/MS t=2.70 [MH$^+$]409. $C_{18}H_{25}{}^{35}ClN_4O$ NMR (DMSO) δ 1.42 (9H, s), 3.14-3.34 (7H, m), 3.62 (2H, s), 6.98 (1H, d), 7.30 (1H, t), 7.60 (1H, d), 8.14 (1H, s), 8.57 (1H, s), 9.90 (1H, brs).

102		(4-*tert* -Butyl-5-(isobutylamino-methyl)-pyrimidin-2-yl]-(3-chloro-phenyl)-amine hydrochloride	LC/MS t=2.88 [MH$^+$]347. $C_1H_{27}{}^{35}ClN_4$ NMR (DMSO) δ 0.89 (6H, d), 1.45 (9H, s), 1.73 (1H, quintet), 2.47 (2H, d), 3.86 (2H, s), 6.95 (1H, d), 7.28 (1H, t), 7.60 (1H, d), 8.13 (1H, s), 8.48 (1H, s), 9.67 (1H, s).
103		(4-*tert* -Butyl-5-[(cyclopropylmethyl-amino)-methyl]-pyrimidin-2-yl}-(3-chloro-phenyl)-amine hydrochloride	LC/MS t=2.81 [MH$^+$]345. $C_{19}H_{25}{}^{35}ClN_4$ NMR (DMSO) δ 0.40-0.45 (2H, m), 0.59-0.64 (2H, m), 1.18 (1H, t), 1.42 (9H, s), 2.99 (2H, q), 4.34 (2H, t), 7.00 (1H, d), 7.31 (1H, t), 7.61 (1H, d), 8.13 (1H, s), 8.72 (1H, s), 9.22 (2H, brs), 9.91 (1H, s)..
104		(3-Chloro-phenyl)-(4-isopropyl-5-piperazin-1-ylmethyl-pyrimidin-2-yl)-amine hydrochloride	$C_{18}H_{24}{}^{35}ClN_5$ NMR (d^6-DMSO) δ 1.25 (6H, d), 2.60-2.92 (3H, m), 3.17-3.82 (8H, m), 7.00 (1H, d), 7.31 (1H, t), 7.64 (1H, t), 8.13 (1H, s), 8.86 (1H, brs), 10.00 (1H, s), 11.70 (1H, brs).

Example 105: (5-Aminomethyl-4-trifluoromethyl-pyrimidin-2-yl)-(3-chloro-phenyl)-amine



A solution of (5-bromomethyl-4-trifluoromethyl-pyrimidin-2-yl)-(3-chloro-phenyl)-amine, (Intermediate 13) (73.2mg) in tetrahydrofuran (3ml) was added dropwise to a stirred mixture of 880 ammonia (2ml) and tetrahydrofuran (5ml). The mixture was stirred at room temperature for 2hrs, evaporated to dryness and re-evaporated from a mixture of dichloromethane and triethylamine. The mixture was taken up in dichloromethane containing a small amount of methanol and chromatographed on silica gel eluting with dichloromethane/methanol 5:1 to give the title compound as a pale yellow solid (31mg).

NMR (DMSO-d6) F1577 δ 2.83 (2H, br s), 3.82 (2H, s), 7.04 (1H, dd), 7.34 (1H, t), 7.66 (1H, dd), 7.99 (1H, m), 8.92 (1H, s), 10.3 (1H, s).

LC/MS CF100425-1, t = 2.45 min, molecular ion observed [M-H]- 301, consistent with $C_{12}H_{10}{}^{35}ClF_3N_4$.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Example 106: Inhalant Formulation

A compound of formula (I) or a pharmaceutically acceptable derivative thereof, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Example 107: Tablet Formulation

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Compound of formula (I) or pharmaceutically acceptable derivative)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

Example 108: Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula (I) in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims: